Tumor induced osteomalacia in head and neck region: single center experience and systematic review

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Abstract

Tumor-induced osteomalacia in the head and neck region remains a challenging diagnosis to manage. Literature pertaining to management and outcome details remains sparse. We describe two cohorts: cohort 1 included seven patients from a single center in Western India with tumors located in paranasal sinuses (n = 3), intracranial (n = 2) and maxilla (n = 2). The unique features from our series is the management of persistent disease with radiation therapy (n = 2) and peptide receptor radionuclide therapy (PRRT) (n = 1). Cohort two has 163 patients identified from 109 publications for systematic review. Paranasal sinuses, mandible, intracranial disease, maxilla and oral cavity, in descending order, are reportedly common tumor sites. Within this cohort, mean age was 46 ± 14 years at presentation with 44.1% having local symptoms. Duration of symptoms varied from 1 to 240 months. Pre-surgery mean serum phosphorus was 1.4 ± 0.4 mg/dL and median FGF-23 levels were 3.6 (IQR:1.8–6.8) times of normal upper limit of normal. Majority (97.5%) were managed primarily with surgical excision; however, primary radiotherapy (n = 2) and surgery combined with radiotherapy (n = 2) were also reported. Twenty patients had persistent disease while nine patients had recurrence, more commonly noted with intracranial and oral cavity tumors. Surgery was the most common second mode of treatment employed succeeded by radiotherapy. Four patients had metastatic disease. The most common histopathological diagnosis reported is PMT mixed connective tissue, while the newer terminology ‘PMT mixed epithelial and connective tissue type’ has been described in 15 patients.

Introduction

Tumor-induced osteomalacia (TIO), also known as oncogenic osteomalacia, is a rare paraneoplastic syndrome caused by overproduction of fibroblast growth factor 23 (FGF23) by a tumor. FGF-23 plays a vital role in renal phosphate handling and vitamin D synthesis. Hence, TIO is characterized by hypophosphatemia due to renal phosphate wasting, inappropriately normal or low 1,25 dihydroxy vitamin D, and elevated or inappropriately normal plasma FGF-23. These biochemical alterations eventually result in osteomalacia. Due to its rarity, the diagnosis of TIO is delayed with the average time from onset of symptoms to diagnosis being more than 2.5 years (1). As a result, patients often present in a debilitated state with multiple fractures, severe muscle weakness.
and loss of height due to skeletal deformities. Even with a high index of suspicion, tumor localization remains challenging as the offending tumor may be very small and can be anywhere in the body. Complete tumor resection remains the mainstay of treatment and is known to result in dramatic resolution of symptoms.

The first case of TIO was reported by Robert McCance in 1947 who treated a patient having low phosphorus levels and bone pain with high doses of vitamin D suspecting her to be a case of ‘vitamin D resistance’; however, the symptoms did not completely resolve until a tumor found in the femur was removed (2). Thereafter, more than 300 cases of TIO have been reported in literature with more than 200 being reported since 2000 (3). The most common tumor site is the lower extremity (>40%) followed by the head and neck region (>20%) (4). There have been several reviews on pathological characters of such tumors but there is no comprehensive review describing clinical characteristics and management of patients with TIO in head and neck region. This article aims to describe a single-center experience with TIO involving the head and neck region followed by a comprehensive clinically oriented review of world literature for the same.

Materials and methods

Cohort 1

Medical records of patients attending Department of Endocrinology, KEM Hospital, Mumbai who were diagnosed with TIO from January 2005 till August 2018 were reviewed after obtaining approval from Institutional Ethical Committee II, Seth G S Medical college and KEM Hospital, Mumbai. Informed consent for the photographs, publication of their clinical details and/or imaging was taken. Patients diagnosed with TIO involving the head and neck region were identified and reviewed for inclusion. Concurrently, patients diagnosed with TIO in other regions, and patients with secondary TIO (3) (including neurofibromatosis, epidermal nevus syndrome, and polyostotic fibrous dysplasia of bone) were excluded from the study.

Diagnosis of TIO was considered in patients presenting with features of hypophosphatemia in absence of relevant family history, evidence of renal phosphate wasting (as demonstrated by low % fractional tubular reabsorption of phosphate (TRP) and tubular maximum for phosphate corrected for glomerular filtration rate (TMP/GFR)) with elevated fibroblast growth factor-23 (FGF-23). Only those patients who had anatomical/functional imaging (CT/MRI or Ga-DOTATATE PET/CT) demonstrating localization of tumor in head and neck region have been included for analysis (n=7).

Biochemical parameters recorded pre-operatively include S. calcium, S. phosphorus, S. alkaline phosphatase (ALP), TMP/GFR, TRP and FGF23 levels, and post-operatively include S. phosphorus and FGF-23 levels. Normal ranges for various parameters at our institute are as follows: S. calcium (9–10.5 mg/dL), S. phosphorus (2.5–5 mg/dL), S. ALP (<117 U/L), TMP/GFR (age- and sex-adjusted values as recommended by Chong et al. (3)), TRP (>85%) and C-terminal FGF-23 (0–150 RU/mL). Furthermore, details from imaging studies done for localization (CT or Ga-DOTATATE PET/CT), treatment modality used, and histopathology reports have been included for analysis. For patients having recurrent disease additional information including time of recurrence following primary management, biochemical profile, localization of recurrent disease and secondary modality of treatment used was documented.

Tubular resorption of phosphate was measured from phosphate and creatinine levels in a spot fasting urine and serum samples at baseline before starting phosphate supplements. TMP/GFR was calculated with use of a nomogram reported by Bijvoet et al. FGF23 was assessed by enzyme-linked immunosorbent assay (GF23 (C-terminal) kit, Immunotopics, Inc, San Clemente, CA, USA). The kit has sensitivity, an intra-assay coefficient of variation (CV), and an inter-assay CV of 30 RU/mL, 5 and 7.3%, respectively. Serum 1,25(OH)2 vitamin D was assessed by radioimmunoassay (RIA), using a DIA source RIA CT kit by DIA source Immunooasays, SA, with an intra-assay CV of 4.5–9.3% (at 77.3 and 24.5 ng/L concentrations, respectively) and inter-assay CV of 11.3–12.7% (at 33.4 and 13.6 ng/L concentrations, respectively). Whole-body (head to toe) scanning with two acquisitions were obtained 1–1.5 h post intravenous injection of 74–111 MBq of DOTATATE labeled with 68Ga. 68Ga was obtained from an in-house 68Ge/68Ga generator. Scans were acquired on a GE Discovery STE PET/CT with 128 x 128 matrix size and 3 min per bed position of iterative algorithm time. The numbers of bed positions were dependent on the height of the patient, usually 10–12 per patient. CT scans were obtained on a 64-slice Phillips Brilliance CT scanner, while MRI scans were performed on a 1.5 tesla Siemens Sonata (Henkestrabe, Germany) MR scanner.
Cohort 2

We searched for all original and review articles in PubMed till June 2019 (Fig. 1). Individual search was carried out for terms ‘Tumour-Induced Osteomalacia’, ‘Oncogenic Osteomalacia’, and ‘Phosphaturic Mesenchymal Tumour’. All original and review articles published in English were reviewed for inclusion. Only publications describing TIO in head and neck region were included. A secondary search for relevant publications was carried out by handsearching through the reference lists of selected publications. Hence, in addition to the cases described in our series, we reviewed 163 index cases from 109 publications of TIO of head and neck region previously reported in literature. Clinical profile, biochemical investigations, imaging modality used for localization, location of tumor, treatment modalities used, histopathology findings, recurrence and its management, and metastasis if any were noted. Whenever serum levels of calcium, phosphorus, parathyroid hormone (PTH), 1,25 (OH)2 vitamin D3 levels were available in SI units, they were converted to conventional units with online calculators for uniformity in documentation. Serum ALP when available in units/liter only was included for analysis, while values reported in any other units were excluded due to non-availability of a suitable conversion method.

Statistical analysis

Statistical analysis was performed using SPSS software version 23.0. Mean (±standard deviation (s.d.)) was used for continuous variables when they were normally distributed and median (interquartile range (IQR)) was used for variables with skewed distribution. The difference between categorical variables was analyzed using chi-square test. P value <0.05 is considered significant.

Results

Cohort 1

This cohort includes seven index patients with TIO involving head and neck region. Their characteristics are described in Table 1. The cohort comprised four males and three females with mean age of 42.7±10.6 years whose tumors were located in paranasal sinuses (n=3), maxilla (n=2), and intra-cranially (n=2). All patients presented with bone pain and muscle weakness, while pathologic fractures (n=4) and local symptoms (n=5) were present in majority of patients. The time lag from onset of symptoms to diagnosis was lengthy (mean: 65.1±50.3 months). In four patients, location of tumor was suspected at initial presentation based on clinical history and examination. Thereafter, tumor location was confirmed with Ga-DOTANOC in two patients, with MRI in one patient and CT in one patient. Three patients were primarily detected on Ga-DOTANOC/DOTATATE PET/CT; one patient had a history of epistaxis elicited retrospectively after tumor localization. Mean tumor size was 3.6±1.3 cm. Except for one patient (who was initially operated at another hospital), pre and post-operative serum phosphorus and FGF-23 levels were available in all patients (Table 1). Three patients were cured with initial surgery, while four had persistent disease. No recurrence was documented in patients cured initially (n=3) over a mean follow-up of 17 months. Out of four patients with persistent disease, one patient was cured with repeat surgery only, two patients were cured with repeat surgery and external beam radiation therapy (EBRT), and one has stable disease after peptide receptor radionuclide therapy (PRRT). Histopathologic findings revealed phosphaturic mesenchymal tumor mixed connective tissue type (PMTMCT) in four patients, while the remaining three patients had PMT-OF (ossifying fibroma like), hemangiopericytoma, and odontogenic fibroma, respectively. Clinical images of case numbers one, five and six are shown in Figs 2, 3 and 4 respectively.
### Table 1 Details of cohort 1 patients.

| Case no. | Age/sex | Location of tumor                  | Clinical features                                                                 | Imaging characteristics | Surgical management | Persistence | Second line modality | Total duration of follow-up | Status | Histopathology |
|----------|---------|-----------------------------------|-----------------------------------------------------------------------------------|-------------------------|--------------------|-------------|----------------------|----------------------------|--------|-----------------|
| 1        | 32/F    | Right maxillary alveolus          | Swelling over right alveolus                                                    | P, F                    | Yes                | Infrastructure maxillectomy | Complete resection | Surgery, RT, PRRT | 48               | Cured  | Odontogenic fibroma |
| 2        | 46/M    | Left petrous tumor                | Earache, protruding mass from left ear                                          | P, MW, F                | No                 | Retromastoid craniotomy with left petrosectomy | No               | IMRT 54 Gy in 30 fractions | 96               | Cured  | Hemangiopericytoma  |
| 3        | 60/M    | Left ethmoid sinus                | Epistaxis                                                                         | P, MW, F                | Yes                | FESS         | Yes                  | FESS 2 times | 36               | Cured  | PMTMCT          |
| 4        | 39/M    | Right frontal & ethmoid sinus     | No                                                                                | P, MW                   | Yes                | Frontal craniotomy and excision | No               | Endoscopic tumor excision | 29               | Cured  | PMTMCT          |
| 5        | 53/F    | Base of the skull                 | No                                                                                | P, MW, F                | Yes                | Retromastoid craniotomy with tumor excision | No               | Yes                  | 13               | Persistence | PMTMCT          |
| 6        | 33/F    | Right maxilla                     | Epistaxis, nasal obstruction                                                      | P, MW                   | Yes                | Right maxillectomy | No               | –                    | 12               | Cured  | PMT OF like      |
| 7        | 36/M    | Right nasal cavity                | Epistaxis                                                                         | P, MW                   | Yes                | Endoscopic endonasal tumor excision | Yes              | –                    | 2                | Cured  | PMTMCT          |

F: fractures; FESS, functional endoscopic sinus surgery; IMRT, intensity-modulated radiation therapy; MW, muscle weakness; NA, not available; OF, ossifying fibroma like; P, pain; PE, physical examination; PMTMCT, phosphaturic mesenchymal tumor mixed connective tissue type; PRRT, peptide receptor radionuclide therapy; RT, radiation therapy.
Cohort 2

This cohort consists of 163 index patients from 109 publications. Pertinent data relevant to index patients is provided in Table 2. Details of clinically relevant parameters are summarized in Table 3. Tests done using two different methods have been tabulated separately in Table 3. Due to heterogeneity in reporting of various parameters, the number of cases included (as denominator) have been specified for each parameter. The mean age was 46 ± 14 years with equal male:female ratio. The reported frequency of tumor sites, in descending order, are paranasal sinuses, mandible, intracranial, maxilla, oral cavity and others. Approximately half the patients (44.1%) had evident local symptoms. Bone pain and muscle weakness were most commonly reported. Late complications of hypophosphatemia such as fractures (61%) and bony deformities including kyphosis/scoliosis with resultant height loss (25.7%) were seen in a significant number of patients. Most patients were diagnosed late in their disease course, despite early access to health care, with median duration from symptom onset being almost 4 years. Out of 163 patients, median elevation of FGF-23 up to 3.6 times ULN has been reported in 55 patients with the interquartile range (IQR) being 1.8–6.8 × ULN. The primary treatment modality was surgery in most

Figure 2
(Case 1): A 32-year-old female presented with bone pains and multiple fractures for 7 years. On examination, approximately 2 cm-sized round swelling in right upper alveolus was seen (A). Preoperative chest radiograph (image contrast adjusted) showing Looser’s zone along lateral border of scapula (arrows) suggestive of osteomalacia (B). Axial contrast-enhanced CT image soft tissue window showing small enhancing lesion in right upper alveolus (arrow) extending from canine to 1st molar tooth causing erosion of right upper alveolus (C). Ga-DOTATATE PET scan showing increased uptake at the level of right maxillary alveolus (arrow) (D). After excision histopathological examination showing tumor comprising of spindle cells with scattered osteoclastic giant cells bearing histologic semblance to giant cell granuloma (odontogenic fibroma) (E) (H&E, 400×).

Figure 3
(Case 5): A 53-year-old female presenting with pain in bilateral groins and difficulty in walking for 3-year duration. As investigations confirmed the diagnosis of FGF-23-dependent hypophosphatemic osteomalacia, 68Ga-DOTATATE PET scan was done to locate the tumor which showed increased uptake in base of skull in left side (dashed arrows) (A). Corresponding axial CT images (B) showing soft tissue density lesion involving occipital bone on left side with erosion of the mastoid and petrous part of adjacent temporal bone. Retromastoid craniotomy with tumor excision was done. Histopathological examination showed hypercellular tumor composed of prominent small blood vessels with areas of hemorrhage (H&E, 200×) (D). Post first surgery repeat 68Ga-DOTATATE scan and corresponding CT images showing residual uptake in base of skull in left side (dashed arrows) in the soft tissue density lesion involving occipital bone on left side with erosion of the mastoid and petrous part of adjacent temporal bone (E). After failed second surgery, patient is now having stable disease after two cycles of PRRT.
patients (97.5%). Two patients with intracranial tumors, who declined surgery, were treated with primary EBRT. Also, two patients received immediate post-operative EBRT for prevention of recurrence due to fear of incomplete tumor removal.

Out of 148 patients for whom outcome data were available; 119 patients had complete initial response to surgery, 20 patients had persistent disease and 9 patients had recurrence as defined by worsening of post-operatively documented normal biochemistry over a variable period of 2–204 months. Patients with persistent/recurrent disease (n=29) were predominantly managed with surgery (65.3%) and/or radiotherapy (30.7%). Among these patients 11 were reported to be alive with no evidence of disease (ANED) and remaining patients were managed with phosphorus supplements with/without other treatment modalities. Four patients had metastatic disease with lymph node and/or lung metastasis. Histopathologically, PMTMCT (48.7%) remains the most commonly reported tumor type followed by hemangiopericytoma (22.7%), PMT of mixed epithelial and connective tissue type (9.4%), giant cell tumor (3.1%) and odontogenic fibroma (3.1%). Other rare types of tumor have been shown in Table 3.

**Discussion**

TIO is a rare and underreported condition due to unawareness about the characteristic clinical and biochemical profile among treating clinicians. Through this study, we aim to highlight our experience with TIO cases involving head and neck region and provide a review of published literature analyzed on a per-patient basis. This will increase awareness and provide valuable insight on critical management issues for this rare diagnosis.

**Cohort 1**

A significant time gap between initial presentation till diagnosis persists even in the presence of local symptoms (1). For any atypical head and neck mass, clinician should enquire into history relevant to osteomalacia, and for a symptomatic patient appropriate biochemistry (S. calcium, S. phosphorus and alkaline phosphatase) should be requested. Vice versa, in a patient with non-localized TIO, a clinician should examine oral and nasal cavities for palpable swellings and enquire about relevant local symptoms.

At our center we carry out a complete biochemical evaluation for TIO which includes calcium studies (S. calcium, S. phosphorus, ALP), TMP/GFR, 1,25 (OH) vitamin D3 and FGF-23 levels. FGF-23 serves as a diagnostic marker as well as an indicator of residual disease or recurrence during long-term follow-up. Thereafter, functional imaging with Ga-DOTANOC PET/CT for localization is done. Its superiority compared to FDG-PET/CT is well established (110, 111, 112). Functional imaging is followed by appropriate anatomic imaging to determine tumor extent and plan for surgical management. Alternatively, in a TIO patient presenting with local symptoms or a mass in head and neck region, anatomic imaging (CT/MRI) followed by biopsy can also be used.
Table 2  Review of published literature on head and neck TIO cases: list of index cases with relevant data.

| Case no. | Author            | Age/sex | Location of tumor                      | Duration of symptoms | Localizing imaging | FGF-23 | Persistence/recurrence | Secondary modality                                      | HPR                           |
|----------|-------------------|---------|----------------------------------------|----------------------|--------------------|--------|------------------------|--------------------------------------------------------|-------------------------------|
| 1        | Renton (5)        | 53 F    | Left ethmoid                           | 60                   | X-ray              | NA     | NA                     | Persistence                                           | Hemangiopericytoma            |
| 2        | Sweet (6)         | 25 F    | Left middle turbinate                  | 12                   | CT                 | NA     | NA                     | No                                                    | Hemangiopericytoma            |
| 3        | Nitzan (7)        | 26 M    | Left mandibular molar legion           | 24                   | X-ray              | NA     | NA                     | No                                                    | Giant cell tumor              |
| 4        | Nomura (8)        | 29 M    | Mandible                               | 24                   | X-ray              | NA     | NA                     | Persistence                                          | RT, chemotherapy, 2nd surgery, chemotherapy         |
| 5        | Linsey (9)        | 54 F    | Right nasopharynx                      | 30                   | CT                 | NA     | NA                     | No                                                    | PMT ossifying fibroma like     |
| 6        | Shunker (10)      | 55 M    | Neck                                   | NA                   | CT                 | NA     | NA                     | No                                                    | PMT                            |
| 7        | Sheshadri (11)    | 40 F    | Ethmoid sinus                          | 24                   | CT                 | NA     | NA                     | No                                                    | Hemangiopericytoma            |
| 8        | Jeffries (12)     | 27 F    | Left maxillary sinus                   | 39                   | CT                 | NA     | NA                     | Persistence                                          | PMT                            |
| 9        | Weidner (13)      | 39 F    | Right maxillary sinus                  | 24                   | CT                 | NA     | NA                     | Recurrence                                           | Repeat surgery                |
| 10       | Papotti (10)      | 38 F    | Nasal cavity                           | 144                  | PE                 | NA     | NA                     | No                                                    | Repeat surgery: partial f/b total laryngectomy f/b RT | Malignant PMT MCT              |
| 11       | Harvey (10)       | 32 F    | Thyroid                                | 144                  | PE                 | NA     | NA                     | Persistence                                          | Repeat surgery                |
| 12       | Lee (14)          | 66 F    | Left nasal cavity                      | 36                   | CT                 | NA     | NA                     | No                                                    | Hemangiopericytoma            |
| 13       | Catalano (15)     | 66 F    | Right maxillary and ethmoidal sinus    | many years           | CT                 | NA     | NA                     | No                                                    | Hemangiopericytoma            |
| 14       | Wilkins (16)      | 55 M    | Left infratemporal mass                | 24                   | CT                 | NA     | NA                     | No                                                    | Sinonasal hemangiopericytoma   |
| 15       | David (17)        | 60 F    | Right subfrontal mass                  | 18                   | CT                 | NA     | NA                     | Recurrence                                           | Medical management            |
| 16       | Kim (18)          | 41 M    | Right upper premolar                   | 48                   | PE                 | NA     | NA                     | No                                                    | Giant cell tumor              |
| 17       | Kim (18)          | 32 F    | Left mandibular molar area             | 96                   | PE                 | NA     | NA                     | No                                                    | Ossifying fibroma              |
| 18       | Avila (19)        | 48 M    | Mandible                               | 60                   | MRI                | NA     | NA                     | No                                                    | Chronic inflammatory tissue with fibrosis and epithelial rests | PMT-MCT                       |
| 19       | Yang (20)         | 31 F    | Left mandible                          | 96                   | CT                 | NA     | NA                     | Patient died of tumor                                | -                              |
| 20       | Gonzalez-Compta (21) | 69 F | Right ethmoido-frontal mass            | 216                  | CT                 | NA     | NA                     | -                                                    | PMT                            |
| 21       | Ohashi (22)       | 43 M    | Left maxillary sinus                   | 14                   | CT                 | NA     | NA                     | -                                                    | Hemangiopericytoma            |
| 22       | Clunie (23)       | 60 F    | Ethmoid sinuses                        | 60                   | CT                 | NA     | NA                     | Recurrence                                           | Medical management            |
| 23       | Sandhu (24)       | 46 M    | Right ethmoid sinus                    | 18                   | CT                 | NA     | NA                     | No                                                    | Hemangiopericytoma            |
| 24       | Reyes-Mugica (25) | 9 F     | Left mandible                          | 1.5                  | MRI                | NA     | NA                     | No                                                    | PMT-MCT                       |

(Continued)
| Case no. | Author          | Age/sex | Location of tumor                    | Duration of symptoms | Localizing imaging | FGF-23 Pre-surgery | FGF-23 Post-surgery | Persistence/recurrence | Secondary modality | HPR                        |
|----------|-----------------|---------|-------------------------------------|----------------------|--------------------|-------------------|--------------------|-----------------------|---------------------|---------------------------|
| 26       | John (27)       | 54 F    | Right frontal, ethmoidal, sphenoid sinuses | NA                   | PE                | NA                | NA                | No                    | Immediate RT          | Malignant Schwannoma    |
| 27       | Reis-Filho (28) | 47 F    | Cavernous sinus                     | 84                   | CT                | NA                | NA                | No                    | Surgery, RT, embolization | Hemangiopericytoma      |
| 28       | Fuentealba (29) | 63 F    | Maxillary sinus                     | 60                   | CT                | NA                | NA                | Persistence           | Hemangiopericytoma      |
| 29       | Ungari (30)     | 24 M    | Ethmoid/sphenoid sinus              | NA                   | NA                | NA                | NA                | No                    | Hemangiopericytoma      |
| 30       | Folpe (10)      | 29 M    | Ethmoid/sphenoid sinus              | 24                   | NA                | NA                | NA                | No                    | Hemangiopericytoma      |
| 31       | Folpe (10)      | 46 M    | Ethmoid sinus                       | 36                   | NA                | NA                | NA                | Recurrence            | Repeat surgery          | Hemangiopericytoma      |
| 32       | Dupe (31)       | 71 M    | Lower mandible                      | 12                   | FDG-PET           | 199 Ru/mL (N <100)| 22 Ru/mL (POD 8)  | No                    | Surgery, RT            | Hemangiopericytoma      |
| 33       | Kaylie (32)     | 46 F    | Temporal bone                       | 120                  | CT                | NA                | NA                | No                    | PMTMCT               |                           |
| 34       | Inokuchi (33)   | 24 F    | Right nasal cavity and paranasal sinuses | 4                    | CT                | NA                | 484 Ru/mL (N: 32–84)| No                    | PMTMCT               |                           |
| 35       | Yoshioka (34)   | 45 M    | Clivus                              | 10                   | MRI               | NA                | 49 pg/mL           | Recurrence            | After first surgery     | Hemangiopericytoma      |
| 36       | Koryama (35)    | 41 F    | Right maxillary sinus               | 36                   | CT                | 309 pg/mL (N: 10–50)| 50 (2 h post surgery)| No                    | PMTMCT               |                           |
| 37       | Elston (36)     | 69 F    | Skull                               | 84                   | Octreoscan        | 67 Ru/mL (N: 3–45)| 32 Ru/mL (3–45) (POD 0)| No                    | PMTMCT               |                           |
| 38       | Beech (37)      | 42 M    | Right ethmoid sinus                 | 84                   | MRI               | NA                | NA                | No                    | Hemangiopericytoma      |
| 39       | Ahn (38)        | 61 M    | Left lower buccal vestibule         | 17                   | PE                | NA                | NA                | No                    | Hemangiopericytoma      |
| 40       | Uramoto (39)    | 48 M    | Tongue                              | 24                   | CT                | NA                | NA                | Recurrence            | Second surgery, RT      | Malignant PMTMCT        |
| 41       | Lewiecki (40)   | 46 M    | Mandible                            | 24                   | Octreoscan        | 262 Ru/mL (N <180)| UD (POD 10)       | No                    | PMT                  |                           |
| 42       | Kenealy (41)    | 79 F    | Left ethmoid sinus                  | NA                   | CT                | 355 U/mL (N: 3–45)| NA                | NA                    | PMTMCT               |                           |
| 43       | Kenealy (41)    | 40 F    | Left ethmoid sinus                  | 60                   | Octreoscan        | 484 U/mL (N: 3–45)| NA                | NA                    | Hemangiopericytoma      |
| 44       | Kyung-In (42)   | 71 F    | Mandible                            | 108                  | PE                | NA                | NA                | No                    | Hemangiopericytoma      |
| 45       | Woo (43)        | 42 F    | Mandible                            | 108                  | PE                | 192 pg/mL (N: 1–71)| 98 pg/mL (POD 11) | Persistence           | PMTMCT               |                           |
| 46       | Savage (44)     | 73 F    | Left maxillary sinus                | 84                   | 111In-pentetreotide | NA                | NA                | No                    | Patient on oral phosphate solution with close follow-up  | Hemangiopericytoma      |
| No. | Author | Age | Gender | Location                          | Modality     | Imaging | Biochemical | Treatment | Comments |
|-----|--------|------|--------|-----------------------------------|--------------|---------|-------------|-----------|----------|
| 47  | Kurien | 45   | M      | Right sphenoid, ethmoid sinus    | CT           | NA      | NA          | PMT-MCT   | NA       |
| 48  | Gupta  | 46   | M      | Nasal cavity                      | FDG-PET     | MRI     | NA          | PMT-MCT   | Persistence |
| 49  | Gore   | 52   | F      | Nasal cavity                      | Octreoscan  | MRI     | 573 Ru/mL   | PMT-MCT   | PMT-MCT  |
| 50  | Kobayashi | 48  | M      | Temporal bone                     | CT           | NA      | NA          | PMT-MCT   | Persistence |
| 51  | Shekhovtsev | 49  | M      | Maxillary sinus                   | MRI         | MRI     | NA          | PMT-MCT   | Persistence |
| 52  | Pedrazzoli | 37  | F      | Right maxillary sinus             | CT           | NA      | NA          | PMT-MCT   | Persistence |
| 53  | Mori    | 42   | M      | Left maxillary sinus              | MRI         | MRI     | 241 pg/mL   | PMT-MCT   | Persistence |
| 54  | Shelekhova | 49  | F      | Maxillary sinus                   | CT           | NA      | NA          | PMT-MCT   | Persistence |
| 55  | Pedrazzoli | 37  | F      | Frontal sinus                     | PE          | PE      | 870 Ru/ml   | Multiple surgeries, cinacalcet | Persistence |
| 56  | Monappa | 35   | M      | Right mandible                    | PE          | PE      | NA          | PMT-MCT   | Persistence |
| 57  | Chokyu | 57   | M      | Middle cranial fossa              | MRI         | MRI     | 84 pg/mL    | PMT-MCT   | Persistence |
| 58  | Chiam   | 55   | M      | Right nasal cavity                | MRI         | MRI     | 232 RU/mL   | PMT-MCT   | Persistence |
| 59  | Cho     | 50   | F      | Nasal cavity, ethmoidal sinus     | CT           | CT      | NA          | PMT-MCT   | Persistence |
| 60  | Uno     | 59   | F      | Right temporal bone               | MRI         | MRI     | >200 pg/mL  | PMT-MCT   | Persistence |
| 61  | Uno     | 61   | M      | Left basi frontalis               | MRI         | MRI     | <3 pg/mL    | PMT-MCT   | Persistence |
| 62  | Andreopoulou | 60  | M      | Right temporal lobe mass          | MRI         | MRI     | 156 pg/mL   | PMT-MCT   | Persistence |
| 63  | Bergwitz | 61   | M      | Mandible                          | PE          | PE      | 870 Ru/ml   | PMT-MCT   | Persistence |
| 64  | Monappa | 62   | M      | Right mandible                    | PE          | PE      | 80 Ru/ml    | PMT-MCT   | Persistence |
| 65  | Chiari  | 64   | M      | Right nasal cavity                | MRI         | MRI     | 232 Ru/ml   | PMT-MCT   | Persistence |
| 66  | Cho     | 65   | M      | F nasal cavity, ethmoid           | CT           | CT      | NA          | PMT-MCT   | Persistence |

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| Case no. | Author | Age/sex | Location of tumor | Duration of symptoms | Localizing Imaging | Secondary modality | Persistence/ recurrence | HPR |
|---------|--------|---------|-------------------|---------------------|-------------------|-------------------|-----------------------|------|
| 72      | Brandwein-Gensler (67) | 66 F | Nasal cavity, maxilla | 24 | PE | NA | Post surgery | NA |
| 73      | Muroz (68) | 60 M | Posterior neck | 24 | PE | NA | Post surgery | NA |
| 74      | Jiang (69) | 37 m | Left nasal cavity | 24 | PE | Octreoscan | No | No |
| 75      | Jiang (70) | 36 F | Mandible | 24 | Octreoscan | Octreoscan | No | No |
| 76      | Jiang (70) | 36 F | Mandible | 24 | Octreoscan | Octreoscan | No | No |
| 77      | Jiang (70) | 28 M | Mandible | 48 | Octreoscan | Octreoscan | No | No |
| 78      | Jiang (70) | 28 M | Mandible | 48 | Octreoscan | Octreoscan | No | No |
| 79      | Jiang (70) | 12 F | Lower gingiva | 120 | Octreoscan | Octreoscan | No | No |
| 80      | Jiang (70) | 45 F | Mandible | 120 | Octreoscan | Octreoscan | No | No |
| 81      | Jiang (70) | 59 F | Mandible | 36 | Octreoscan | Octreoscan | No | No |
| 82      | Jiang (70) | 69 F | Mandible | 8 | Octreoscan | Octreoscan | No | No |
| 83      | Jiang (70) | 81 F | Mandible | 102 | Octreoscan | Octreoscan | No | No |
| 84      | Jiang (70) | 84 F | Nasal sinus | 48 | Octreoscan | Octreoscan | No | No |
| 85      | Jiang (70) | 84 F | Nasal sinus | 48 | Octreoscan | Octreoscan | No | No |
| 86      | Jiang (70) | 86 F | Nasal sinus | 102 | Octreoscan | Octreoscan | No | No |
| 87      | Jiang (70) | 87 M | Nasal sinus | 102 | Octreoscan | Octreoscan | No | No |
| 88      | Mathis (72) | 28 F | Cribiform plate | 36 | MRI | CT | NA | NA |
| 89      | Mathis (72) | 32 M | Anterior cranial fossa, ethmoid sinus | 48 | SVS | Octreoscan | NA | NA |
| 90      | Tarasevich (73) | 40 F | Right maxillary sinus | 36 | MRI | CT | NA | NA |
| 91      | Papierska (74) | 40 F | Right maxillary sinus | 36 | MRI | Octreoscan | NA | NA |
| 92      | Lee (75) | 60 F | Right maxillary sinus | 72 | MRI | Octreoscan | NA | NA |
| 93      | Alexander (76) | 49 M | Right maxillary sinus | 48 | MRI | Octreoscan | NA | NA |
| 94      | Annamalai (77) | 35 F | Right maxillary sinus | 180 | MRI | Octreoscan | NA | NA |
| 95      | Okamitani (78) | 35 F | Right maxillary sinus | 8 | MRI | Octreoscan | NA | NA |
| 96      | Annapoorni (5) | 50 F | Right maxillary sinus | 6 | MRI | Octreoscan | NA | NA |
| 97      | Mohi (79) | 40 M | Right maxillary sinus | 12 | MRI | Octreoscan | NA | NA |
| 98      | Fernández-Cococket (80) | 3 M | Maxilla and mandible | 6 | MRI | Octreoscan | NA | NA |
| 99      | Fatihali (81) | 49 F | Right frontal lobe | 36 | MRI | Octreoscan | NA | NA |
| No. | Name       | Age | Gender | Anatomical Site                  | Imaging   | Age/Stage | Histology                      | Follow-Up                                                                 |
|-----|------------|-----|--------|----------------------------------|-----------|----------|--------------------------------|---------------------------------------------------------------------------|
| 100 | Ray (82)   | 35  | M      | Left nasal cavity                | CT        | 24       | NA                             | -                                                                         |
| 101 | Qari (83)  | 60  | M      | Gingiva of mandibular teeth      | PE        | 72       | NA                             | Hemangiopericytoma                                                        |
| 102 | Wasserman (84) | 50 | M      | C3 vertebrae                     | NA        | 24       | NA                             | -                                                                         |
| 103 | Wasserman (84) | 33 | F      | Nose, lips, tongue               | NA        | 120      | NA                             | Malignant PMT MCT                                                          |
| 104 | Mani (85)  | 56  | M      | Occipital bone                   | PE        | 36       | 129.97 pg/mL (N: 33.9-51.6)    | -                                                                         |
| 105 | Yu (86)    | 37  | M      | Maxilla                          | PE        | 36       | 64.9 pg/mL                      | PMT                                                                       |
| 106 | Yu (86)    | 50  | M      | Mandible                         | PE        | 6        | 312.84 pg/mL (N: 33.9-51.6)    | Spindle cell tumor with PMT features PAMT                                  |
| 107 | Yu (86)    | 50  | M      | Left nasal cavity                | Octreoscan| 72      | 272.71 pg/mL (N: 33.9-51.6)    | PMT                                                                       |
| 108 | Yu (86)    | 38  | F      | Left nasal cavity and ethmoid sinus | Octreoscan | 12     | 350.9 pg/mL (N: 33.9-51.6)     | PMT                                                                       |
| 109 | Takashi (87) | 77 | M      | Left parotid gland               | FDG-PET   | 96       | 186.9 pg/mL                     | -                                                                         |
| 110 | Gresham (88) | 42 | M      | Ethmoid mass                     | MRI       | 36       | NA                             | Glomangioma                                                               |
| 111 | Agaimy (89) | 48 | M      | Nasal cavity                     | NA        | NA       | NA                             | Cellular, nondescript                                                     |
| 112 | Lee (90)   | 33  | M      | Right mandible                   | Ga-DOTANOC| 156     | 86.7 pg/mL (N: 10-50)           | Giant cell granuloma                                                      |
| 113 | Lee (90)   | 52  | M      | Left ethmoid sinus               | Ga-DOTANOC| 6       | 492.3 pg/mL (N: 10-50)          | Meningioma                                                               |
| 114 | Schober (91) | 59 | F      | Right frontobasal region         | SVS       | 22       | 1600 Ru/mL (N: 26-110)          | -                                                                         |
| 115 | Zuo (92)   | NA  | M      | Left parotid gland               | Octreoscan| 36      | NA                             | PMT                                                                       |
| 116 | Zuo (92)   | NA  | F      | Left maxillary bone              | FDG-PET   | 36      | NA                             | -                                                                         |
| 117 | Hana (93)  | 38  | M      | Bilateral ethmoid sinus          | MRI       | 84       | 120 pg/mL (N: 10-50)            | Hemangiopericytoma                                                       |
| 118 | Chanukya (94) | 31 | M      | Left nasal cavity                | Ga-DOTANOC| 24      | 1310 Ru/mL (N: 0-150)           | -                                                                         |
| 119 | Gonzalez (95) | 42 | M      | Nasofrontal sinus                | PE        | 72       | 75.9 pg/mL (N: 8-54)            | PMT                                                                       |
| 120 | Singh (96) | 67  | M      | Posterior wall of mastoid antrum | Ga-DOTANOC| 204     | 237 Ru/mL (N: 0-150)            | -                                                                         |
| 121 | Singh (96) | 45  | M      | Left side of body of mandible    | Ga-DOTANOC| 12      | 1553 Ru/mL (N: 0-150)           | PMT                                                                       |
| 122 | Pelletier (97) | 37 | M      | Mandible                         | SVS f/b MRI| NA      | 310 Ru/mL (N: 19-114)           | -                                                                         |
| 123 | Pelletier (97) | 49 | F      | Mandible                         | Octreoscan of growing lesion on MRI with FDG-avidity and gradient on SVS | NA      | 1194 Ru/mL (N: 19-114)          | -                                                                         |

(Continued)
| Case no. | Author     | Age/sex | Location of tumor | Duration of symptoms | Localizing imaging | FGF-23                  | Persistence/recurrence | Secondary modality                  | HPR                        |
|----------|------------|---------|-------------------|----------------------|--------------------|------------------------|------------------------|-------------------------------|--------------------------|
| 125      | Villepelet (99) | 41 F    | Right ethmoid sinus | NA                   | CT                 | NA                     | 48 pg/mL (POD-5)        | No                           | PMT                       |
| 126      | Pelo (100)     | 62 F    | Left TMJ          | 60                   | PE                 | NA                     | NA                     | No                           | PMT                       |
| 127      | He (101)      | 54 F    | Right parotid     | 24                   | Ga-DOTANOC         | NA                     | NA                     | No                           | Salivary basal cell adenoma |
| 128      | Wu (102)      | 49 F    | Right mandible    | 216                  | NA                 | NA                     | Persistence            | Multiple surgeries          | Odontogenic fibroma        |
| 129      | Wu (102)      | 20 F    | Left maxilla      | 48                   | NA                 | NA                     | No                     | Odontogenic fibroma        | PMT of mixed epithelial & connective tissue type |
| 130      | Wu (102)      | 30 F    | Right maxilla     | 60                   | NA                 | NA                     | NA                     | Persistence                | Odontogenic fibroma        |
| 131      | Wu (102)      | 36 M    | Left mandible     | 60                   | NA                 | NA                     | NA                     | No                           | PMT of mixed epithelial & connective tissue type |
| 132      | Wu (102)      | 25 M    | Right maxilla     | 72                   | NA                 | NA                     | NA                     | No                           | PMT of mixed epithelial and connective tissue type |
| 133      | Wu (102)      | 15 F    | Right mandible    | 24                   | NA                 | NA                     | NA                     | No                           | PMT of mixed epithelial and connective tissue type |
| 134      | Wu (102)      | 41 M    | Right mandible    | 60                   | NA                 | NA                     | NA                     | No                           | PMT of mixed epithelial and connective tissue type |
| 135      | Wu (102)      | 34 M    | Left maxilla      | 72                   | NA                 | NA                     | NA                     | No                           | PMT of mixed epithelial and connective tissue type |
| 136      | Wu (102)      | 50 M    | Right mandible    | 18                   | NA                 | NA                     | NA                     | No                           | PMT of mixed epithelial and connective tissue type |
| 137      | Wu (102)      | 66 M    | Right maxilla     | 108                  | NA                 | NA                     | NA                     | No                           | PMT of mixed epithelial and connective tissue type |
| 138      | Wu (102)      | 26 M    | Left maxilla      | 36                   | NA                 | NA                     | NA                     | No                           | PMT of mixed epithelial and connective tissue type |
| 139      | Wu (102)      | 32 M    | Right maxilla     | 36                   | NA                 | NA                     | NA                     | No                           | PMT of mixed epithelial and connective tissue type |
| 140      | Wu (102)      | 41 M    | Right mandible    | 60                   | NA                 | NA                     | NA                     | No                           | PMT of mixed epithelial and connective tissue type |
| 141      | Wu (102)      | 22 M    | Right mandible    | 24                   | NA                 | NA                     | NA                     | No                           | PMT of mixed epithelial and connective tissue type |
| 142      | Wu (102)      | 31 M    | Right maxilla     | 36                   | NA                 | NA                     | NA                     | No                           | PMT of mixed epithelial and connective tissue type |
| No | Patient | Age | Gender | Site | Procedure | Pathology | SUV Max | SUV Avg | SUV Min | SUV SD | SUV | SUV | SUV | SUV | SUV | SUV | SUV | SUV | SUV | SUV | SUV | SUV | SUV | SUV | SUV | SUV | SUV | SUV | SUV | SUV | SUV | SUV | SUV | SUV | SUV | SUV | SUV | SUV | SUV | SUV | SUV | SUV | SUV | SUV | SUV | SUV | SUV | SUV | SUV | SUV | SUV | SUV | SUV | SUV | SUV | SUV | SUV | SUV | SUV | SUV | SUV | SUV | SUV | SUV | SUV | SUV | SUV | SUV | SUV | SUV | SUV | SUV | SUV | SUV | SUV | SUV | SUV | SUV | SUV | SUV | SUV | SUV | SUV | SUV | SUV | SUV | SUV | SUV | SUV | SUV | SUV | SUV | SUV | SUV | SUV | SUV | SUV | SUV | SUV | SUV | SUV | SUV | SUV | SUV | SUV | SUV | SUV | SUV | SVM
### Table 3  Summary of literature review.

| Parameter                                           | Value                  | No. of patients with available data |
|-----------------------------------------------------|------------------------|------------------------------------|
| Age (years) (mean ± s.d.)                           | 46 ± 14                | 160                                |
| Sex                                                 | 81:81                  | 162                                |
| Location of tumor % (no.)                           |                        |                                    |
| Paranasal sinuses                                   | 43.7 (76)              |                                    |
| Mandible                                            | 21.5 (34)              |                                    |
| Intracranial                                        | 11.8 (19)              |                                    |
| Maxilla                                             | 9 (13)                 |                                    |
| Oral cavity                                         | 6.2 (10)               |                                    |
| Skull                                               | 1.2 (2)                |                                    |
| Parotid                                             | 1.3 (2)                |                                    |
| Posterior neck                                      | 1.3 (2)                |                                    |
| Cervical vertebra                                   | 1.3 (2)                |                                    |
| Intratemporal fossa                                 | 0.7 (1)                |                                    |
| Mastoid antrum                                      | 0.7 (1)                |                                    |
| Thyroid                                             | 0.7 (1)                |                                    |
| Local symptoms % (no.)                              | 44.1 (49)              | 111                                |
| Hypophosphatemic symptoms                           |                        |                                    |
| Muscle weakness % (no.)                             | 77.9 (106)             | 136                                |
| Fractures % (no.)                                   | 61.2 (68)              | 111                                |
| Bone pains % (no.)                                  | 100 (142)              | 142                                |
| Bony deformities % (no.)                            | 25.7 (27)              | 105                                |
| Duration of symptoms (months), median (IQR)         | 36 (24–72)             | 139                                |
| Biochemical profile                                 |                        |                                    |
| S. Calcium (mg %) (mean ± s.d.)                     | 8.9 ± 0.5              | 87                                 |
| S. Phosphorus (mg %) (mean ± s.d.)                  | Pre-op                 | 1.4 ± 0.4                          | 119                                |
| Post-op                                             | 3 ± 0.7                | 62                                 |
| S. Alkaline phosphatase (U/L) (median (IQR))        | 313 (200–420)          | 95                                 |
| TMP/GFR (median (IQR))                              | 0.9 (0.6–1.3)          | 39                                 |
| TRP (median (IQR))                                  | 61 (46.2–72.2)         | 21                                 |
| PTH (pg/mL) (median (IQR))                          | 55.9 (39.3–83.7)       | 73                                 |
| 1,25 (OH)2 vitamin D3 (pg/mL) (median (IQR))        | 18 (8.2–26.2)          | 46                                 |
| FGF-23 (Pre-op) (median (IQR))                      | X ULN                  | 3.6 (1.8–6.8)                      | 55                                 |
| C-terminal (Ru/mL)                                  | 573 (234–1058)         | 33                                 |
| Intact (pg/mL)                                      | 256 (131–393)          | 22                                 |
| FGF-23 (Post-op)                                    | C-terminal (Ru/mL)     | 69.3 (36.5–138)                    | 18                                 |
| Intact (pg/mL)                                      | 14 (5.9–50)            | 15                                 |
| Tumor size (cm) (median (IQR))                      | 2.5 (1.8–3.2)          | 70                                 |
| Localization imaging % (no.)                        | History and PE         | 16.7 (22)                          |                                    |
| X-ray                                               | 2.3 (3)                |                                    |
| CT scan                                             | 25.9 (34)              |                                    |
| MRI                                                 | 10.6 (14)              |                                    |
| Octreotide scintigraphy                             | 20.6 (27)              |                                    |
| FDG-PET/CT                                          | 8.4 (11)               |                                    |
| Ga-DOTA-based PET/CT                                 | 11.4 (15)              |                                    |
| Selective venous sampling of FGF-23                 | 3.8 (5)                |                                    |
| Primary modality of treatment % (no.)                | Surgery                | 97.5 (156)                         | 160                                |
| Radiation therapy                                   | 1.2 (2)                |                                    |
| Combined surgery + radiation therapy                | 1.2 (2)                |                                    |
| Complete response to primary treatment % (no.)       | 80.4 (119)             | 148                                |
| Persistent disease % (no.)                          | 13.5 (20)              | 148                                |
| Follow-up (months)                                  | 13 (5.2–36)            | 108                                |
| Recurrence % (no.)                                  | 7 (9)                  | 128                                |
| Time to recurrence (months) (range)                  | 2–204                  |                                    |

(Continued)
Complete surgical removal with wide margin of excision remains the cornerstone of management in these cases (3). This is particularly difficult in intracranial tumors resulting in persistent disease as noted in both our patients with intracranial tumors.

S. Phosphorus and FGF-23 levels are used for post-operative surveillance. Half-life of FGF-23 is very short and one can document it immediately post-operatively (93). Persistent elevation of FGF-23 was noted post-operatively in two patients (cases 1 and 6), which normalized on re-evaluation after 3 months. This observation has been previously reported particularly with C-terminal FGF-23 assay (108, 109). Phosphate supplements are discontinued post-operatively to allow for surveillance. Reimaging is performed in patients with persistent symptoms and biochemically active disease.

In recurrent or persistent cases, complete tumor removal resulted in cure in two patients, hence, this remains the preferred approach at our institute. In inoperable cases, two patients received external beam radiotherapy (EBRT) and one patient received peptide receptor radiotherapy (PRRT). In one patient (Case 2) EBRT was given after first surgery due to difficult tumor location at petrous apex. He had a gradual and complete response to RT over next 4 years. In another scenario (case 3), the patient had persistent disease after functional endoscopic sinus surgery (FESS) for left ethmoid sinus tumor. Following two repeat FESS, patient was considered for EBRT for persistent disease. Patient received IMRT 54 Gy in 30 fractions. S. Phosphorus and FGF-23 normalized gradually over one and half years and this patient who was previously bedbound is now walking without any support.

One patient (case 5) in our cohort has received PRRT for persistent disease after two surgeries for base of skull tumor (113). As tumor was Ga-DOTATATE avid having

| Parameter                                         | Value            | No. of patients with available data |
|---------------------------------------------------|------------------|-------------------------------------|
| Site wise persistence/recurrence % (no./no.)      |                  |                                     |
| Paranasal sinuses                                 | 14.4 (7/4)       | 76                                  |
| Mandible                                          | 17.6 (6/0)       | 34                                  |
| Intracranial                                      | 36.8 (4/3)       | 19                                  |
| Maxilla                                           | 7.6 (1/0)        | 13                                  |
| Oral cavity                                       | 33.3 (1/2)       | 10                                  |
| Thyroid                                           | 100 (1)          | 1                                   |
| Secondary modality of treatment % (no.)            |                  |                                     |
| Surgery                                           | 65.4 (17)        | 26                                  |
| RT                                                | 30.8 (8)         |                                     |
| Chemotherapy                                      | 7.7 (2)          |                                     |
| Cinacalcet                                        | 7.7 (2)          |                                     |
| Octreotide                                        | 7.7 (2)          |                                     |
| Radiofrequency ablation                           | 3.8 (1)          |                                     |
| PRRT                                              | 3.8 (1)          |                                     |
| Others                                            | 3.8 (1)          |                                     |
| Metastasis % (no.)                                | 2.7 (4)          | 148                                 |
| Histopathology % (no.)                            |                  | 158                                 |
| PMT MCT                                           | 48.7 (77)        |                                     |
| PMT ossifying fibroma like                        | 1.3 (2)          |                                     |
| PMT mixed epithelial and connective tissue type   | 9.5 (15)         |                                     |
| Malignant PMT MCT                                 | 3.2 (5)          |                                     |
| Hemangiopericytoma                                | 22.8 (36)        |                                     |
| Giant cell tumor                                  | 3.2 (5)          |                                     |
| Odontogenic fibroma                               | 3.2 (5)          |                                     |
| Glomangiopericytoma                               | 2.5 (4)          |                                     |
| Malignant schwannoma                              | 0.6 (1)          |                                     |
| Meningioma                                        | 0.6 (1)          |                                     |
| Salivary basal cell adenoma                       | 0.6 (1)          |                                     |
| Ameloblastic fibrosarcoma                         | 0.6 (1)          |                                     |
| Primitive mesenchymal tumor                       | 0.6 (1)          |                                     |
| Arteriovenous hemangioma                          | 0.6 (1)          |                                     |
| Spindle cell tumor with PMT features              | 0.6 (1)          |                                     |
| Cellular non-descript                             | 0.6 (1)          |                                     |
| Chronic inflammatory tissue with fibrosis and epithelial cell rests | 0.6 (1) | |
Krenning score IV, patient was considered for PRRT after a thorough discussion in a multidisciplinary meeting. This patient has stable disease after two cycles of PRRT with 150–200 uCi $^{177}$Lu-DOTATATE.

PMTMCT remains the commonest histopathologic entity in these patients. We also reported one patient for each of the following: PMT-OF like, odontogenic fibroma and hemangiopericytoma in our cohort. Detailed histopathological findings for cases three, four and six have been published previously (114).

Although the sample size of cohort 1 was small, the epidemiological data are similar to cohort 2. There is an increased prevalence of local symptoms at presentation and higher rate of persistence following primary surgery at our center. This could be attributed to referral bias to a tertiary care center.

**Cohort 2**

Here we present a detailed review of published English literature for TIO cases involving head and neck region ($n=163$) (5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109). This is the largest series of its kind published to date.

**Epidemiology**

As is the case with overall TIO literature, almost equal male:female ratio is reported in head and neck TIO patients (3). Middle age is the most common age at presentation and three pediatric cases are reported so far. TIO is a difficult diagnosis in pediatric patients as heritable hypophosphatemic rickets is a more likely diagnosis unless the tumor is evident. Fernández-Cooke et al. have reported a 3-year-old child with rickets and a jaw tumor. Two years went by before a link was established between the two and a diagnosis of TIO was made (80). In the case described by Reyes-Mugica et al. the heightened awareness of pediatric endocrinologist for this condition led to early screening with imaging and subsequent surgical removal resulting in cure within 6 weeks of onset of symptoms (25). In the third case reported by Wu et al. also the duration of hypophosphatemic symptoms was 2 years (102).

The time from symptom onset to final diagnosis remains dreadfully long. In this series of cases of TIO involving head and neck region, only 10% ($n=14$) were diagnosed in the first year of disease onset with majority of them having local symptoms at presentation. Feng et al. observed a misdiagnosis rate of 95.1% with 240 case-times of misdiagnoses among 144 cases of TIO even in the presence of evident hypophosphatemia in 43.1% cases (115). Reasons cited for misdiagnosis were disease rarity, insidious onset, nonspecific clinical manifestations and poor recognition by the clinician. Presence of local compressive symptoms and/or swelling in approximately 50% patients in this review highlights the problem of delayed or missed diagnosis as musculoskeletal symptoms are ignored until presentation with advanced local symptoms.

**Biochemical profile**

The typical biochemical profile in TIO is straightforward: hypophosphatemia with normocalcemia, moderately elevated ALP, normal PTH, inappropriately normal-to-high urinary phosphate excretion, low serum 1,25 (OH)$_2$ vitamin D3 and elevated FGF-23 levels (3).

FGF-23 is useful as a tumor marker. Based on two case reports, half-life of FGF-23 is between 20–50 min (116, 117). More recently, Hana et al. reported half-life of FGF-23 to be 18.5 min in a patient with intracranial PMTMC using intact FGF-23 assay (93). This allows FGF-23 to be used for intraoperative monitoring to determine the extent of tumor removal. Immediate post-op decline in FGF-23 levels within normal range is reported by other investigators (36, 47, 51, 59) as well. Elston et al. reported discordant increase in C-terminal FGF-23 post-op which has not been confirmed by other studies (36). As previously stated, persistent elevation in C-terminal FGF-23 in immediate post-operative period has been documented despite complete tumor removal (108, 109). With no reports on levels of other postulated phosphotonins like matrix extracellular phosphoglycoprotein (MEPE) and secreted frizzled-related protein 4 (SFRP4) in patients with TIO, their role still remains unclear (118).

**Location of tumor**

Most common site for TIO in head and neck region is paranasal sinuses. Among them, ethmoid sinuses are the most common site followed by maxillary, sphenoid and frontal sinuses. Most common tumors are PMTMC, hemangiopericytoma and glomangiopericytoma, in descending order. The second most common site is bony tumors arising from the mandible and maxilla with...
odontogenic fibroma and, PMT of mixed connective tissue and epithelial components as special tumor types. Third position is for intracranial tumors involving anterior cranial fossa, middle cranial fossa, and posterior cranial fossa, in descending order of prevalence. Reported tumors include PMTMC, hemangiopericytoma and meningioma. Tumors of oral cavity include gingival tumors (molar/premolar), tongue and buccal vestibule in that order of occurrence. Apart from PMTMC (including malignant) and hemangiopericytoma, tumors from this region also include giant cell tumor and ossifying fibroma. Rarely tumors have been reported from skull, parotid glands, posterior neck, infratemporal fossa, mastoid antrum, thyroid and vertebra.

**Localization imaging**

Classically, history of local compressive symptoms and/or visible mass on physical examination is instrumental in diagnosing TIO even in this current era of sensitive imaging modalities. Earlier clinicians were dependent on physical examination and x-rays for diagnosing TIO. Renton *et al.*, Nitzan *et al.*, and Nomura *et al.* have localized head and neck TIO through x-rays alone (5, 7, 8). With the introduction of CT scans (1980–2000), 60% tumors in the head and neck region were localized with this modality. The first localization of head and neck TIO on MRI was reported by Avila *et al.* in 1996 using MR skeletal survey (19).

Following *in vitro* demonstration of somatostatin receptors (SSTRs) by Reubi *et al.* (119), scintigraphic studies using 111In-pentetreotide for tumor localization was published by De Beur *et al.* in 2002 (120). Subsequently, localization with 99mTc-MIBI and FDG-PET scans was reported (121, 122). Use of FDG-PET was limited due to poor specificity of non-receptor-based imaging, and slow-growing nature of these tumors resulting in false-negative results (96). With improved spatial resolution, lower radiation dose and more rapid whole-body tomographic imaging of PET/CT studies in comparison to scintigraphy, 68Ga-DOTA-based PET/CT scans became the investigation modality of choice in TIO patients (112, 123). Various studies have shown superiority of 68Ga-DOTATATE PET/CT and 68Ga-DOTANOC PET/CT over FDG-PET/CT and Octreoscan for tumor localization in TIO (110, 111, 112). The largest such study is that of 54 patients by Zhang *et al.* using 68Ga-DOTATATE PET/CT reported 100% sensitivity and 90.9% specificity in lesion detection (124). Use of positron emitter radiotracer 68Ga enabling PET-based imaging along with higher affinity SSTR ligands like DOTATATE (SSTR 2,3,5) and DOTANOC (SSTR 2,3,5) are postulated to be responsible for enhanced sensitivity of 68Ga-DOTA-based PET/CT over Octreoscan (112). Thereafter, Singh *et al.* highlighted the issue of multiple low-grade benign uptakes using 68Ga-DOTANOC PET/CT especially at fracture sites and described the use of SUVmax and anatomical imaging showing soft tissue component in the lesion to pinpoint the causal lesion (96). In summary, Ga-DOTA-based PET/CT is superior to other functional studies like FDG-PET and Octreoscan, but its utilization will depend on local availability and expertise (119).

Selective venous sampling of FGF-23 has been studied for accurate localization of TIO. Kobayashi *et al.* used selective venous sampling as an initial guiding modality localizing the tumor to right head and neck region, although on retrospect distortion of right external ear canal was noted and no prior functional imaging was done to localize the tumor (48). Andreopoulou *et al.* reported sensitivity of 87% and specificity of 71% at FGF-23 concentration ratio of 1.6 between the venous drainage of the tumor bed and general circulation after sampling 17 major veins and their branches (60). They concluded that selective venous sampling is not useful in the absence of suspicious lesion on imaging studies and its use should be limited to cases with multiple suspicious sites or before resection in anatomically challenging cases. In 2017, Lee *et al.* reported contrasting results. In their cohort, five patients negative on both 111Indium-octreotide scintigraphy and FDG-PET/CT were subjected to selective blood sampling from 10 to 14 sites (90). They identified the culprit lesion on follow-up with targeted MRI or whole-body Ga-DOTATOC in four patients. Tarasova *et al.* and Shober *et al.* have used selective venous FGF-23 sampling to confirm the SSTR expressing meningioma to be the FGF-23 secreting culprit lesion as many meningiomas are avid on SSTR-based imaging but may not be the source of FGF-23 (73). In summary, in the current era of SSTR-based imaging, the role of this modality seems to be limited to cases with multiple suspicious uptake sites, intracranial lesions consistent with meningioma, and lastly in imaging negative cases to identify a target for focused follow-up imaging.

**Treatment**

**Primary modality**

Complete surgical resection with adequate wide margin remains the treatment of choice in these tumors (3). This is supported in head and neck TIO cases where anatomical
sites less amenable for this approach have higher persistence or recurrence rate for example intracranial tumors. Hana et al. also reiterated this principle in their report on recurrent anterior skull base tumor with en bloc tumor removal followed by filling of the large skull base defect with pedicle subgaleal flap resulting in absence of recurrence over 25-month follow-up (93).

Stereotactic radiotherapy has been described in two cases as primary modality. Both patients had frontal lobe tumors and both refused surgery. One patient had lower plasma FGF-23 and oral phosphorous requirement at 6-month follow-up. The details of RT are not described in this case report (60). The second patient received 60 Gy of fractionated stereotactic radiotherapy over 5 weeks (73). On follow-up, patient was off phosphorus supplement and had normal FGF-23 concentration after 4 years. The tumor was stable with areas of multiple small hemorrhages. BMD improved by approximately 50% with no evident new fracture. As the tumors are slow growing, radiotherapy is deemed to be less effective (3).

Surgery combined with adjuvant post-op radiotherapy was used by John et al. in a case of invasive ‘malignant schwannoma’ (27). Over 2.5 years of follow-up, serum phosphorus normalized but 1,25(OH) vitamin D3 was persistently low. MRI showed no evidence of residual/recurrent tumor. Similarly, Lee et al. described a case where the patient received post-operative radiotherapy following incomplete removal of an ethmoid tumor, which resulted in normal serum phosphorus with no residual tumor on MRI after completion of RT (90).

In summary, although complete surgical excision remains the treatment modality of choice, in rare cases radiation therapy can be used with an expectant slow response.

**Persistent/recurrent disease**

Persistent/recurrent disease signifies failure of complete resection of the tumor after primary excision. This occurs more commonly in intracranial disease and oral cavity lesions where en bloc tumor removal is challenging and leads to higher surgical morbidity and complications. Serial biochemical follow-up is essential as true recurrences after complete biochemical resolution are known, but usually it is the recurrence of symptoms which brings the disease to surface.

After anatomic imaging to confirm the site of tumor recurrence, re-exploration of the surgical site along with attempted en bloc removal remains the preferred approach. Out of eleven patients with persistent/recurrent disease who have ANED on follow-up, eight have been treated with re-surgery alone.

In persistent cases multiple re-surgeries, radiotherapy, cinacalcet and octreotide have been used with limited success. Seufert et al. reported a patient with left thigh TIO localized on octreotide scintigraphy having complete resolution of phosphaturia and normalization of serum phosphorus with 50–100 µg of octreotide thrice a day in preoperative setting (125). However, this initial success has not been replicated in subsequent studies (34, 126). Extrapolating from patients with hypoparathyroidism with elevated FGF-23 and serum phosphorus levels, Gellers et al. advocated for the use of cinacalcet in the treatment of TIO (127). But development of hypercalciuria and hypocalcemia limits the use of cinacalcet in this cohort. Disease stability with dasatinib has been reported (55). As these tumors also express SSTR, PRRT remains a potentially useful option in tumors showing Krenning III/IV uptake on 68Ga-DOTATATE PET/CT (113). It has been more than a decade of successful utilization of two radiopeptides 90Y-DOTATOC and 177Lu-DOTATATE for treatment of advanced neuroendocrine tumors (NETs) (128). After binding to SSTR these peptides are internalized in tumor cells and the released breakdown products in lysosomes mediate radioactivity-induced local damage (128). Apart from our case, we could not find any other experience with PRRT in TIO literature. In patients with persistent disease, treatment with oral phosphate supplements and calcitriol is continued for symptomatic improvement.

**Metastases**

Four cases of malignant TIO in head and neck region are reported so far. Three of them originated from oral cavity and one from mandible. Uramoto et al. described a case of malignant PMTMCT involving tongue with lymph node metastases treated with two surgeries followed by radiation therapy with persistent disease on last follow-up (39). Bergwitz et al. reported a patient with ameloblastic fibrosarcoma of mandible with pulmonary and lymph node metastases (61). Patient had multiple recurrences and was managed with repeated surgeries, and lastly cinacalcet with persistent hypophosphatemia. Fatani et al. reported an interesting case of malignant PMTMCT arising from oral cavity who after 17 years of follow-up developed lung metastases which were resected in addition to multiple surgeries for primary disease (71). Patient was normophosphatemic on follow-up. The fourth case of malignant PMTMCT was reported by Wasserman et al. (84).
The tumor involved nose, lip and mouth. No further follow-up/management details have been reported.

**Histopathology**

Weidner et al. initially proposed the term phosphaturic mesenchymal tumors (PMT) and their classification into four distinct subtypes: (I) mixed connective tissue variant (MCT), (II) osteoblastoma like, (III) Non-ossifying fibroma type, (IV) ossifying fibroma like (129). In 2004, Folpe et al. reviewed all previously published cases and found that they all belong to PMTMCT category (10). In this review we have reported the revised diagnosis as mentioned by Folpe et al. In 2018, Wu et al. described a new entity called “PMT mixed epithelial and connective tissue type” which is found exclusively in alveolar bone of maxilla and mandible (102). They found this tumor to be common in males and in patients <40 years of age. They have proposed a revised diagnosis of previously published six cases to this new entity, but we have reported them according to the original report. Apart from PMTs, other reported tumors in head and neck region causing TIO include meningioma, salivary basal cell adenoma, malignant schwannoma, ameloblastic fibrosarcoma, and spindle cell tumor with PMT features.

**Study limitations**

To our knowledge this is the largest review of TIO due to tumors located in head and neck region till date. The per-patient analysis method used in this study with minute detailing of all clinically relevant published aspects is the major strength of this study. There are several limitations in this study. As the review is a retrospective analysis of published case reports, all the limitations pertaining to retrospective studies apply to it. Additionally, many case reports lacked important clinical details as majority of them focused on pathology or imaging. A meticulous attempt was made to include all published literature regarding the subject but a few studies may not have been included.

**Summary**

TIO in the head and neck region is a rare disorder that warrants management by a multidisciplinary team including an endocrinologist, head and neck surgeon, radiologist, nuclear physicist and pathologist. Low phosphorus with elevated FGF-23 levels in a patient with clinical features of osteomalacia and/or mass in the head and neck region should be evaluated with Ga-DOTA-based PET/CT imaging. An alternative approach would be anatomical imaging followed by biopsy in a patient with local symptoms and clinically apparent swelling. Complete surgical excision with wide margin is of utmost importance in these cases resulting in dramatic clinical and biochemical normalcy. Clinical and biochemical follow-up is necessary even after documented cure as true recurrences have been reported. Whenever complete excision is not achieved, repeat surgical excision is recommended for accessible disease burden. In inoperable cases, radiotherapy, PRRT and medical management are suitable alternatives which should be decided by a multidisciplinary team on an individual basis. Although the tumor remains benign in most cases, one must remain vigilant in case of long-standing disease due to the reported risk of metastasis. Histopathological examination in most cases reveals PMTMCT, but other types are also seen.

**Declaration of interest**

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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