



Case report

FDG PET-CT missed tibial metastasis in head and neck cancer, case report and systematic review

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ABSTRACT

Introduction: Head and neck squamous cell carcinoma (HNSCC) is the seventh most common type of cancer in the world. Metastases occur in up to 40 % of cases and bones are the second most frequent site. Metastases in extremities are uncommon with very few publications covering distal lower-limb bone metastasis.

Case presentation: Here we report the case of a patient with HNSCC managed by induction chemotherapy, surgery and adjuvant chemo-radiotherapy. During the adjuvant treatment, the patient presented pain in the right tibia, with additional workup revealing a distal lower-limb bone metastasis which had remained undetected during the recommended standard workup for HNSCC.

Discussion: Current guidelines request that FDG PET-CT is performed down to the popliteal fossae. The undetected metastasis led to overtreatment of the patient. Systematic review of the literature showed only six cases of head and neck cancer's distal lower-limb metastasis which are eligible for discussion.

Conclusion: Although rare, physicians should keep in mind that as recommended FDG PET-CT does not extend below the popliteal fossae, metastases could be missed and therefore lead to inappropriate treatment.

1. Introduction

Head and Neck Squamous Cell Carcinoma (HNSCC) is the seventh most common type of cancer. It is estimated that up to 40 % of HNSCC patients will develop metastasis during the course of their disease. [1–3]. Lungs are the most common site of metastasis, (60–70 % of cases), followed by the spine (4–23 %), non-cervical lymph nodes (15.5 %), and liver (13 %) [4,5].

Bone metastasis is not uncommon in HNSCC, axial skeleton is affected in 85 % of cases, including the spinal column, ribs, pelvis, humerus, and proximal femur. Tibial metastasis is infrequent and has been rarely described in HNSCC to our knowledge [6,7].

FDG PET-CT has replaced bone scintigraphy since 2014 for the detection of bone metastasis and current guidelines request that FDG PET-CT is performed down to the popliteal fossae [8]. Here we report a case of a patient with an HNSCC who developed a tibial metastasis missed at the FDG PET-CT during the recommended workup. This case

report has been reported in line with the SCARE criteria and the work has been reported in line with the PROCESS criteria [9,10].

2. Case report

A 47-year-old man presented with a few months' history of painful swelling of the left gonial angle. He also complained of generalized weakness and reported unquantified weight loss. The patient is an active heavy smoker (>30 pack-years). Intra-buccal examination highlighted teeth mobility, a swelling of the left vestibule and induration of the mouth's floor with an erythematous mucosa. Cervical palpation revealed two fixed and indurated lymph nodes on the left, level III. Orthopantomogram (OPG) showed a pathological fracture of body of the mandible (Fig. 1.a). Histology reported a squamous cell carcinoma with p16 negative status. A complete workup was carried out with head and neck CT scanner and MRI, chest CT scan, FDG PET-CT. It showed two cervical ipsilateral lymphadenopathies and did not highlight distant

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lesions. The patient was discussed at a multidisciplinary team meeting, the disease was staged cT4aN2bM0. Due to a poor performance status (performance status ECOG 2 and severe malnutrition), the patient was deemed unfit for surgery. The multidisciplinary team decided to start the treatment with induction systemic platinum-based chemotherapy. In addition, supportive care has been initiated with a nutritionist for renutrition by feeding tube, a psychologist and pain management specialist. After three months, evaluation showed a partial metabolic response without new lesions, the patient's general condition improved allowing surgical care to proceed (ECOG-PS 1). A mandibulectomy associated with bilateral neck dissection (level I-IV) and reconstruction with a vascularized fibular free flap was performed. (Fig. 1.b) Pathological staging confirmed ypT4aN2bM0R0 (three metastatic lymph nodes, including one with capsular rupture). Indication of adjuvant radio-chemotherapy was set.

Early after the onset of radiotherapy, the patient started complaining of increasing pain in his right knee without known traumatic event. X-ray of the knee was performed and reported an unspecific lesion.

(Fig. 2a) Two months later the pain worsened and was present at rest, increased at any mobilization associated with swelling and caused nocturnal awakenings. A new X-ray was performed and showed a pathological fracture associated with an osteolytic lesion of the proximal tibia (Fig. 2b). MRI and bone biopsy confirmed the metastasis of squamous cell carcinoma of the oral cavity. An extended FDG PET-CT (Fig. 3) was requested and revealed a hypermetabolic lesion in the tibial medial plateau. Due to the pathological fracture and poor probability of bone healing, resection of the tibial lesion associated with arthrodesis of the right knee by mega-prosthesis was performed. This intervention improved patient pain. After appropriate physiotherapy, he regains his weight-bearing ability and was able to walk without help. Five weeks after surgery, due to systemic progression, Nivolumab (anti-PD1 antibody) was initiated but did not offer results. The patient was referred to a palliative care unit. The patient died a few months later.

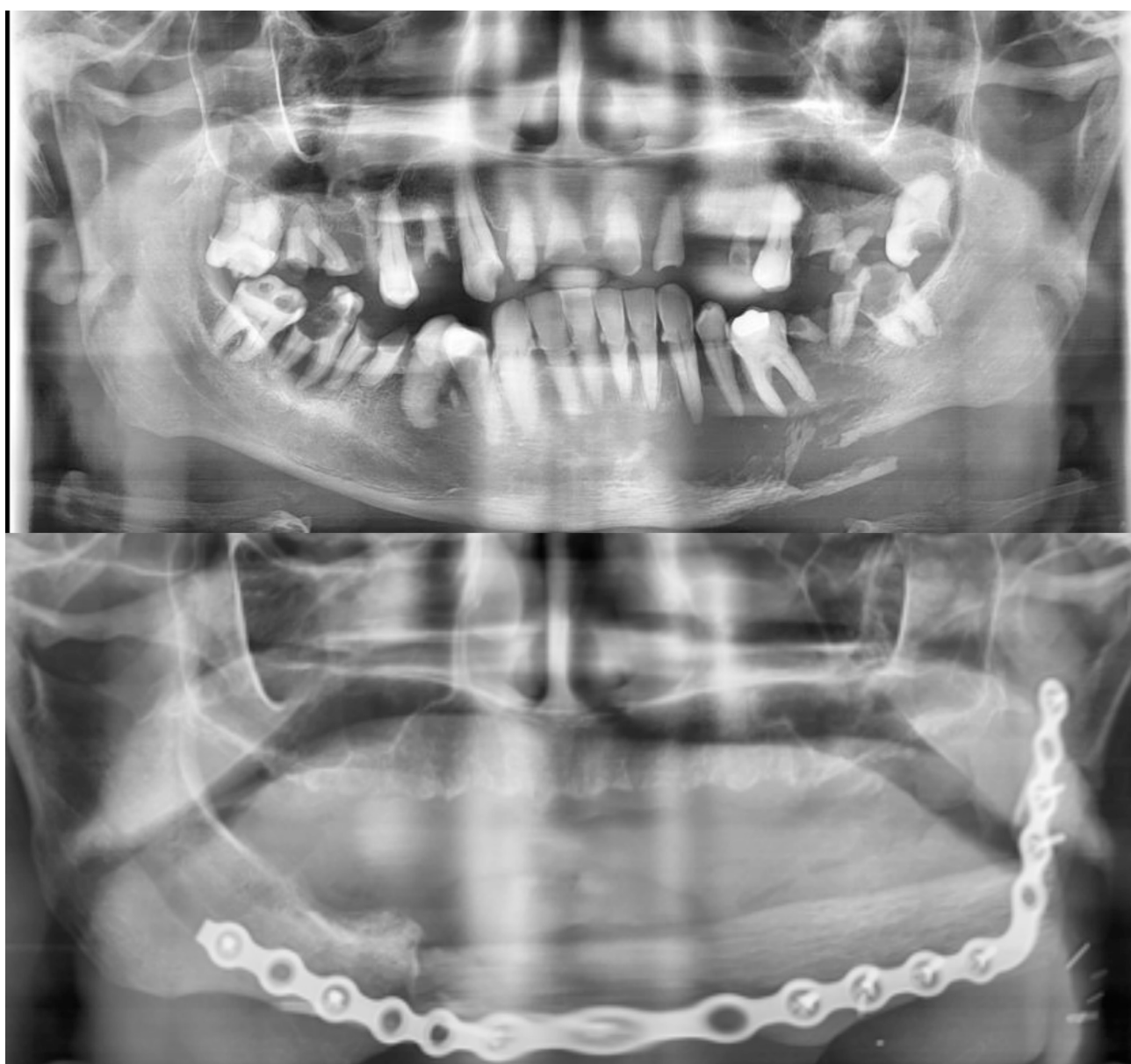


Fig. 1. Orthopantomogram before chemotherapy treatment (a). Showing pathological fracture with poor dental status. Orthopantomogram after surgery (b). Showing a fibular free flap with a reconstruction plate in place.



Fig. 2. (a) X-ray of the right knee. Firstly, reported with unspecific lesion. (b) X-ray of the right knee. Showing pathological proximal tibial fracture with osteolytic lesion and soft tissue swelling. Heterogeneous bone structure suggestive of bone dystrophy.

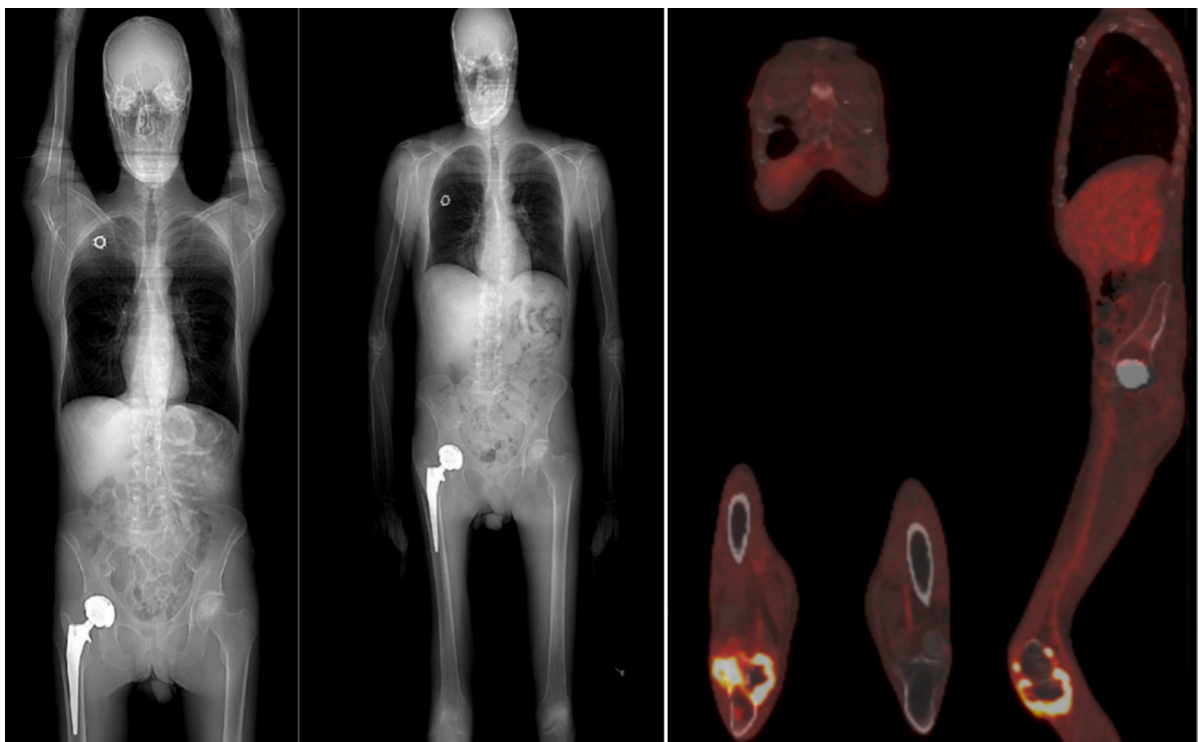


Fig. 3. (a) recommended FDG-PET scout: extends from the base of the skull to the upper third of the thigh. (b) extended FDG-PET scout after discussion with the nuclear radiologist to extend beyond the popliteal fossae. (c): extended FDG-PET: showing an intensely hypermetabolic range of the right tibial plateau (SUV max 18.19 with central hyperuptake).

3. Discussion

Lower limb bone metastases, such as tibial metastases are considered rare, even for cancers with preferential bone dissemination [8,11]. Tibial metastases are often discovered at an advanced stage of the disease or at recurrence, mostly associated with kidney or thyroid cancer [6,7]. A current hypothesis about the mechanism behind bone metastasis is 'red marrow bone homing' with precocious tumor cells found in red marrow bone which were disseminated after an unknown stimulus. This can explain the preferential HNSCC metastasis localization to the bones, such as the spine, ribs and pelvis and the rarity of metastasis in extremities which contain yellow marrow [12].

Bone metastases significantly affect the patient's prognosis and therapeutic decision [13]. Sixty-three percent of bone metastasis is asymptomatic, 20 % are painful, and 3 % are associated with neurological symptoms [7]. Tibial metastases have an important impact in terms of function and mobility, compared to other sites of metastasis in the axial skeleton [14]. Once pathological fractures have occurred, bone healing is compromised, and surgery is often required. Pathological fractures generally worsen the patient's quality of life and increase mortality [15]. Therefore, early detection and management may improve patients' quality of life [16]. In our case, early detection of the tibial metastasis could have led to another decision from the multidisciplinary team and spared a major surgery.

Since 2014 the National Comprehensive Cancer Network recommends for locally advanced HNSCC, FDG PET-CT and chest-CT for the screening of distant metastases [17]. FDG PET-CT have a high diagnosis accuracy for distant metastases [18,19] with good sensibility (>88 %) and specificity (97 %) in bone metastases detection [20,21]. Bone scintigraphy leads to a high percentage of equivocal findings and is no more routinely performed for staging HNSCC [22]. Bone scintigraphy is therefore no longer recommended. According to the 2014 recommendation, FDG PET-CT in head and neck cancer extends from the base of the skull to the upper third of the thigh. It does not run beyond the distal end of the femur [21]. Bone metastases located beyond this point are therefore not systematically investigated and this could explain the low reported incidence.

The literature covering the epidemiology of lower limb bone metastasis, all types of cancer combined, is limited to case reports or small series. We performed a systematic review of the literature about lower limb metastasis of head and neck cancer and highlighted 31 articles. The methodology is detailed in the [Appendix](#).

Among these 31 articles, we excluded 25 for different reasons: some do not concern head and neck cancers (10 relevant to thyroid cancers, 3 to esophageal cancers, one cutaneous cancer, one renal cancer, breast cancer) and some do not concern bone metastases of the lower limb (1 cerebral metastasis, 1 humerus metastasis), or 7 for concerning others subject. Finally, 6 articles were retained as eligible and each reported one case ([Table A](#)). Two cases were about squamous cell carcinoma from the larynx three were about salivary gland tumours and one was about squamous cell carcinoma from oral cavity. All patients were male, and age ranged from 23- to 70-years-old. Five bone metastases were diagnosed during the follow-up and one at initial workup. When documented, pain is the symptom that revealed the metastases.

Localizations were femoral diaphysis (1), femoral collar (2), patella (2) and tibia (1). Every patient underwent a biopsy before treatment. Ended given the rarity of bone metastases in the lower limbs, this biopsy remains to confirm the diagnosis. One patient benefited from surgery of the metastasis alone, two from radiotherapy only, two from surgery associated with radiotherapy like our patient, and two cases have no mentioned treatment.

Following this literature review, we did not find any case report concerning a patient presenting with tibial metastasis associated with HNSCC. The only tibial lesion is due to a mixed malignant tumor of the

palate and revealed by a bone scan in 2001 [26]. This lesion was found at early stage and would have been missed by current recommended assessment.

4. Conclusion

To our knowledge we report the first case of tibial metastasis from squamous cell carcinoma of the oral cavity. Although rare, physicians should keep in mind that as recommended FDG PET-CT does not extend below the popliteal fossae, metastases could be missed and therefore lead to overtreatment. Physicians must be vigilant for new symptoms presenting in the distal lower limbs.

CRediT authorship contribution statement

Vanden Haute Noémie: principal author
 Vervaeet Catherine: principal co author
 Maindiaux Laure: co-author and interpretation
 Taylor Stephen: traduction and interpretation
 Durieux Valerie: data collection and analysis
 Holbrechts Stephan: study concept and interpretation

Consent

The patient died, and we had no family members recorded in our data. I have the agreement of the head of the hospital to publish this case report.

CHU HELORA, site Kenedy - Mons, Belgium

Ethical approval

The patient died, and we had no family members recorded in our data. I have the agreement of the head of the hospital to publish this case report.

CHU HELORA, site Kenedy - Mons, Belgium

Guarantor

Vanden Haute Noémie
 Holbrechts Stephan

Table A

Published case reported of lower limb bone metastasis of head and neck cancer.

Reference	Primary tumor	Histology	P16	Age	Gender	Symptoms	Imaging	Time at diagnose from initial treatment	Metastatic site	Treatment of metastasis	Survival (year from metastasis)
2019, Anila, K. et al. [23]	Buccal mucosae	Squamous cell carcinoma	NR	62	Male	Pain	CT	8 m	Femur (upper diaphysis)	RT	No
2018 Wong, W. K. and D. Vokes [24]	Larynx	Squamous cell carcinoma	NR	63	Male	Pain	CT	10 m	Femur (center of diaphysis)	S	No
2008 Hunter, J. et al. [25]	Palate	Low grade papillary adenocarcinoma	NR	70	Male	NR	NR	21 y	Femur (upper diaphysis)	S + RT	Yes (22y)
2001 Aynaci, O., et al. [26]	Salivary gland	Malignant mixed tumor	NR	23	Male	Pain	BS	not reported	Tibia	S + RT	Yes (1y)
2000 Yun Sun Choi et al. [27]	Larynx	Squamous cell carcinoma	NR	65	Male	Pain and induration	MRI	1 y	Patella	Not reported	No
1993 Kawamura, H., and al. [28]	Gingival salivary gland	Carcinoma (not specified)	NR	37	Male	Pain	CT	4 y	Patella medial condyle	RT	Yes (2y)
2023 Vanden Haute, N., et al. (*)	Buccal mucosae	Squamous cell carcinoma	P16 +	47	Male	Pain	MRI	6 m	Tibia	S + RT	No

Abbreviation: NR: Not Reported; BS: bone scintigraphy; CT: computed tomography months; y: years; S: Surgery; RT: Radiotherapy.

Research Registration Number

1. Name of the registry:
2. Unique identifying number or registration ID:
3. Hyperlink to your specific registration (must be publicly accessible and will be checked):

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Appendix A

A literature search was conducted and updated last on July 2023 using the Ovid Medline and SciVerse Scopus databases. This research was performed by a scientific librarian experienced in searching for medical and scientific publications and two readers independently selected eligible abstracts before a consensus.

The “PICO” (population, intervention, comparator, outcome) model for clinical questions was used to identify the concepts included in the questions. The corresponding search criteria of “P” and “I” were translated into MeSH terms, and free-text keywords that were searched for in text word fields in Medline and in titles, abstracts and keywords in Scopus.

List of MeSH terms and free-text keywords used to search Ovid Medline database:

Database: Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid Medline® Daily and Ovid Medline® 1946-present.

P Criterion: Head and neck cancer: (exp “Head and Neck Neoplasms”/ OR neck neoplasm*.tw OR head neoplasm*.tw OR neck cancer*.tw OR head cancer*.tw OR Upper Aerodigestive Tract Neoplasm*.tw OR UADT Neoplasm*.tw OR Esophag* Neoplasm*.tw OR Esophag* cancer*.tw OR Esophag* Squamous Cell Carcinoma*.tw OR Facial neoplasm*.tw OR Facial cancer*.tw OR eyelid neoplasm*.tw OR eyelid cancer* OR mouth neoplasm*.tw OR mouth cancer*.tw OR oral neoplasm*.tw OR oral cancer*.tw OR gingival neoplasm*.tw OR gingival cancer*.tw OR lip neoplasm*.tw OR lip cancer*.tw OR palatal neoplasm*.tw OR palatal cancer*.tw OR salivary gland neoplasm*.tw OR salivary gland cancer*.tw OR Salivary Gland Lymphadenoma*.tw OR sebaceous Lymphadenoma*.tw OR parotid neoplasm*.tw OR parotid cancer*.tw OR Sublingual Gland Neoplasm*.tw OR Sublingual Gland cancer*.tw OR Submandibular Gland Neoplasm*.tw OR Submandibular Gland cancer*.tw OR tongue neoplasm*.tw OR tongue cancer*.tw)

I Criterion: lower limb metastasis: (tibial.tw OR tibia.tw OR Femur.tw OR femoral.tw OR foot.tw OR feet.tw OR patella.tw OR patellar.tw OR fibula.tw OR fibular.tw OR knee.tw) ADJ3 metastas*.tw

Legend: term/ = MeSH term (with all the possible subheading combinations). TITLE-ABS-KEY() = terms are searched in the title, the abstract and the keywords * = stands for zero or more characters.

List of free-text keywords used to search Scopus database

P Criterion: Head and neck cancer: TITLE-ABS-KEY (“neck neoplasm*” OR “head neoplasm*” OR “neck cancer*” OR “head cancer*” OR “Upper Aerodigestive Tract Neoplasm*” OR “UADT Neoplasm*” OR “Esophageal Neoplasm*” OR “Esophageal cancer*” OR “Esophageal Squamous Cell Carcinoma*” OR “Facial neoplasm*” OR “Facial cancer*” OR “eyelid neoplasm*” OR “eyelid cancer*” OR “mouth neoplasm*” OR “mouth cancer*” OR “oral neoplasm*” OR “oral cancer*” OR “gingival neoplasm*” OR “gingival cancer*” OR “lip neoplasm*” OR “lip cancer*” OR “palatal neoplasm*” OR “palatal

cancer*” OR “salivary gland neoplasm*” OR “salivary gland cancer*” OR “Salivary Gland Lymphadenoma*” OR “sebaceous Lymphadenoma*” OR “parotid neoplasm*” OR “parotid cancer*” OR “Sublingual Gland Neoplasm*” OR “Sublingual Gland cancer*” OR “Submandibular Gland Neoplasm*” OR “Submandibular Gland cancer*” OR “tongue neoplasm*” OR “tongue cancer”*)

I Criterion: lower limb metastasis: TITLE-ABS-KEY((tibial OR tibia OR Femur OR femoral OR foot OR feet OR patella OR patellar OR fibula OR fibular OR knee) W/3 metastas*)

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