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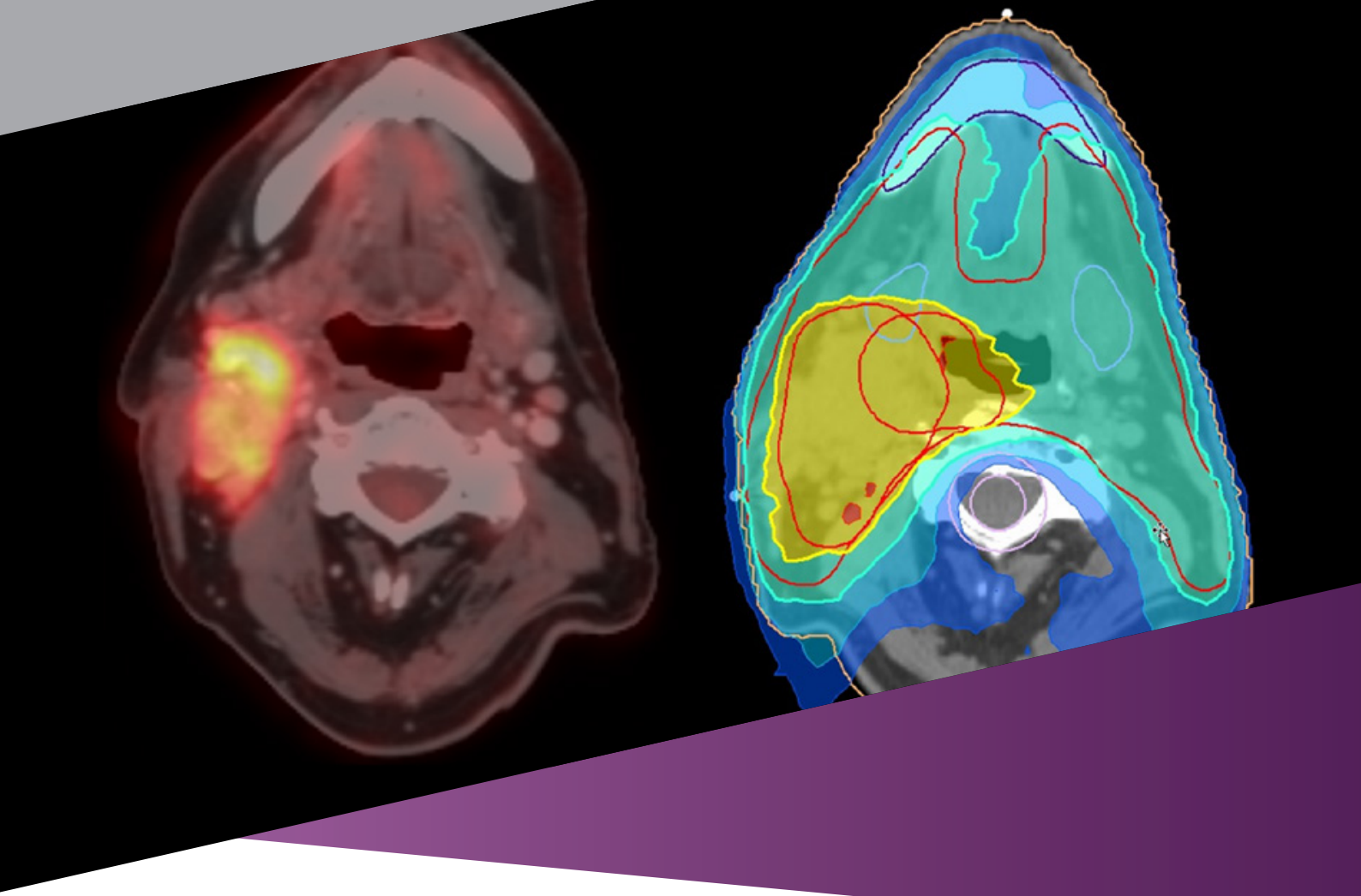
Positron Emission Tomography (PET) in Head & Neck Cancers



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Head and neck cancer

Introduction

Positron emission tomography-computed tomography (PET/CT) is an advanced molecular imaging technique used for diagnose, stage, and survey various cancers. PET is used primarily to assess physiology, while CT is used primarily to assess anatomy. This paper focuses on the use of PET/CT application for head and neck cancers.

Squamous cell carcinomas make up 95% of primary head and neck cancers, (excluding thyroid/parathyroid tumors and paragangliomas). Human papillomavirus infection is a significant factor in the development of these cancers. [^{18}F]FDG PET/CT is crucial in pre-treatment staging, radiotherapy planning, treatment response assessment, and post-treatment follow-up(1).

Staging

The conventional staging of Head and Neck Squamous Cell Carcinoma **(HNSCC)** involves physical examination, endoscopy, and CT scans. MRI is sometimes added for assessing oral cavity and paranasal sinus cancers. However, [^{18}F]FDG PET/CT offers advantages over morphological imaging methods, particularly in assessing neck lymph nodes, potential distant metastases, and second primaries. [^{18}F]FDG PET/CT is more accurate than conventional imaging for detecting metastatic foci and identifying distant metastases or second primary tumors. In a study, [^{18}F]FDG PET/CT improved the TNM classification of the disease and altered the management of 13.7% of HNSCC patients. National Comprehensive Center Network updated the clinical practice guidelines for [^{18}F]FDG PET/CT imaging of head and neck cancer in 2023, recommending the use of [^{18}F]FDG PET/CT for initial staging of certain HNSCC types(2, 3).

Response to therapy

[^{18}F]FDG PET/CT is useful in evaluating residual disease following radiotherapy or chemotherapy for HNSCC. Structural imaging techniques like CT/MRI have limitations in accurately identifying viable tumor within residual masses and small tumor deposits. [^{18}F]FDG PET/CT is advantageous for treatment response assessment as it is a functional imaging approach and does not rely on morphological changes. [^{18}F]FDG PET/CT scan has shown high sensitivity and specificity to detect residual/recurrent lesions after chemotherapy and radiotherapy treatment. Focal and asymmetric [^{18}F]FDG uptake with intensity greater than surrounding normal tissues suggests residual disease, while diffuse [^{18}F]FDG uptake within the radiation field is an indicator of post-radiation inflammation. [^{18}F]FDG PET/CT is recommended 12 weeks post-treatment for assessment of residual or recurrent disease(4).

Radiotherapy planning

PET/CT with [^{18}F]FDG is useful for radiation planning in HNSTC patients, allowing for better selection and delineation of target volumes and dose planning. [^{18}F]FDG PET/CT is more effective than diagnostic CT without contrast media in defining tumor volume and modifies staging and radiotherapeutic planning in up to one-third of untreated HNSTC patients. PET/CT also improves the selection of candidates for curative and palliative radiation therapy. A study found that [^{18}F]FDG PET/CT imaging led to modification in radiation treatment planning in 13.7% of untreated primary HNSSC patients, demonstrating its effectiveness in improving radiotherapy planning.

Follow up

The need and frequency of post-treatment imaging assessment for HNSCC patients are still controversial. It is unclear whether patients with distant relapse but no symptoms benefit from early detection of the disease. However, early detection of locoregional recurrence may improve survival by facilitating timely salvage treatment. A meta-analysis study found that [^{18}F]FDG PET/CT had higher sensitivity and negative predictive value for locoregional recurrence than conventional imaging. The authors recommended that the initial [^{18}F]FDG PET/CT scan should be performed within 6 months after completion of treatment and the next routine PET scan for subclinical patients with an initial negative PET result should be done 1 year after the initial PET scan.

Head and Neck cancer of unknown origin

Patients with head and neck metastasis without a detectable primary tumor are diagnosed as unknown primary tumor in the head and neck. Metastases to the oral soft tissues may manifest as a submucosal or gingival mass. Clinical presentation includes swelling, pain, and paresthesia. Radiographic presentation is mainly radiolucent with a poorly defined border.

[^{18}F]FDG PET/CT is used as a diagnostic tool in this context, and the treatment for such a tumor can involve neck dissections, tonsillectomies, and radiation therapy for all mucosal sites and both sides of the neck. Identifying the primary tumor is important for targeted treatment, which can improve survival chances and lower morbidity by better targeting treatment options, including surgery, and decreasing the field of irradiation. Studies have shown that [^{18}F]FDG PET/CT is highly effective in locating primary tumors, with significantly higher sensitivity for detection of occult primary tumors compared to CT or combined CT and MRI in patients with cervical metastasis from an unknown primary tumor(5).

Oral cancer classification

The WHO/IARC classification of oral cancers includes the oral cavity, oropharynx, cancer of the salivary glands, and odontogenic tumors. This classification highlights the significant pathological differences between OSCC (oral squamous cell carcinoma) and OPC (oropharyngeal carcinoma). Tumors of the ropharynx (base of the tongue, tonsils, and adenoids) are further categorized as either HPV-positive or HPV-negative SCC (squamous cell carcinoma).

1- MALIGNANT TUMORS OF THE SALIVARY GLANDS

Malignant salivary gland tumors are uncommon but can occur in various locations. They often present as painless masses and can cause facial paralysis or tongue-tie. The exact cause is unknown, but radiation exposure is a risk factor.

Imaging with [^{18}F]FDG PET/CT helps in diagnosis and staging (detecting perineural tumor spread and intraparotid nodal metastases). [^{18}F]FDG PET/CT showed similar accuracy to conventional imaging studies in predicting primary tumors and more accuracy for lymph node and distant metastasis.

Higher SUV_{max} and SUV entropy indicate poorer survival. [^{18}F]FDG PET/CT is useful for recurrent cases to determine disease extent and guide treatment decisions(6).

2- ODONTOGENIC TUMORS

Odontogenic neoplasms can be classified as malignant or benign and originate from remnants of tooth germs. These tumors are extremely rare.

There is limited knowledge about the metabolic features of these tumors and the usefulness of FDG PET/CT scan for staging and follow-up. Clear cell odontogenic carcinoma (CCOC) shows variable [^{18}F]FDG uptake, while ameloblastic carcinoma exhibits increased metabolic activity. Further research is needed to assess [^{18}F]FDG PET/CT scan sensitivity in odontogenic tumor(7).

3- MALIGNANT TUMORS OF THE JAW

Malignant jaw lesions can be of hematopoietic or bone origin, including lymphoma, multiple myeloma, osteosarcoma, chondrosarcoma, and Ewing sarcoma. Metastases to the jaw are common in patients with a history of breast, prostate, gastrointestinal, or renal carcinoma. Osteosarcoma is the most frequent jaw malignancy, typically presenting as a mass with pain and sensory disturbances. Radiographic appearance varies, with a characteristic “sun-ray appearance.”

[^{18}F]FDG PET/CT is useful for staging, monitoring response to therapy, and predicting prognosis in osteosarcoma. It is also accurate in diagnosing chondrosarcoma and detecting recurrence of Ewing sarcoma. [^{18}F]FDG PET/CT findings can guide clinical decision-making and predict disease progression and treatment response(8).

4- SARCOMAS OF THE SOFT TISSUES

Oral soft tissue sarcomas are rare (1% of all oral malignancies). Subtypes include fibrosarcoma, malignant fibrous histiocytoma, liposarcoma, rhabdomyosarcoma, leiomyosarcoma, angiosarcoma, and alveolar soft part sarcoma.

[^{18}F]FDG PET/CT scan allows for more accurate staging of advanced soft tissue sarcomas (STSs), influencing the choice of surgical resection and impacting prognosis. Lower baseline metabolic tumor volume (MTV)/total tumor volume (TTV) and progression in interim [^{18}F]FDG PET/CT are associated with lower survival (9).

5- NASOPHARYNGEAL CARCINOMA

Nasopharyngeal carcinoma (NPC) is a relatively uncommon cancer, more prevalent in East and Southeast Asia. Common symptoms include ear pain and neck mass.

[^{18}F]FDG PET/CT imaging improves the staging of NPC compared to MRI and can guide treatment decisions. Deep learning PET/CT-based radiomics shows promise for prognosis prediction and

individualized chemotherapy. [^{68}Ga]-FAPI PET/MR is effective in detecting primary tumors and potential metastases, particularly in the skull and brain. Further research is needed to evaluate its use in assessing lymph nodes and distant metastases(10).

6- MUCOSAL MELANOMA

Mucosal melanomas (MMs) are rare and aggressive cancers that primarily affect the conjunctiva, nasal cavity, paranasal sinuses, and oral cavity. They have a poor prognosis and their biology is not well understood.

PET/CT imaging with [^{18}F]FDG is highly sensitive for staging non-cutaneous melanomas and can impact treatment decisions, especially for metastatic lesions.

7- HEAD AND NECK MALIGNANT DISEASE IN HIV/AIDS

AIDS increases the risk of the development of neoplastic disease. Kaposi Sarcoma (KS) is a multicentric neoplastic proliferation of endothelial cells and was very common prior to antiretroviral therapies (ART) and often representing the first sign of progression to AIDS. KS is associated with the (HHV-8). KS can involve any oral site, but most frequently involves the attached mucosa of the palate and gingiva, or the dorsum of the tongue.

PET tracers beyond FDG for Head and Neck malignancies

As mentioned before, in cases of head and neck cancer of unknown primary (HNCUP); the most common primary sites are lung, kidney, liver, and prostate for men, and breast, female genital organs, kidney, and colorectal for women. Prostate and breast metastases are mainly concentrated in the jaws rather than the soft oral tissues.

[^{18}F]FDG PET/CT outperforms CT and MRI in identifying the primary tumor, with a detection rate of 25%–69%. Nevertheless, some limitations hamper the application of [^{18}F]FDG PET/CT in primary tumor identification for HNCUP. Physiologic [^{18}F]FDG uptake can be seen in any lymphatic structure (e.g. Waldeyer's ring), salivary glands and brown fat. Also, infection and chronic inflammation (e.g., nasopharyngitis and gingivitis) can also result in high [^{18}F]FDG uptake. Such limitations may lead to false-positive findings, with a rate of 16%–25%. False-negative [^{18}F]FDG uptake can be seen in small, mucinous, well-differentiated, and necrotic lesions. Therefore, novel specific radiopharmaceuticals with low background uptake in the head and neck are needed to improve the detection rate of the primary tumor in HNCUP.

Recently, [^{68}Ga]-radiolabeled fibroblast activation protein inhibitor (FAPI), a novel FAP-targeted PET tracer, has shown great value in the diagnosis of diverse carcinomas. Several studies have demonstrated that [^{68}Ga]-FAPI revealed high uptake in primary tumors with low background noise in the head and neck region. These promising findings indicate that [^{68}Ga]-FAPI could serve as a potential alternative to [^{18}F]FDG for the assessment of head and neck cancers. Notably, higher image contrast of [^{68}Ga]-FAPI PET/CT may result in more precise radiotherapy planning for head and neck tumors. Therefore, future research on more patients should be considered to evaluate the clinical value of [^{68}Ga]-FAPI PET.

[^{68}Ga]-PSMA PET/CT is a valuable imaging modality which has been extensively studied in prostate cancer. [^{68}Ga]-PSMA PET/CT analysis in a series of patients with head and neck adenoid cystic

carcinoma showed tracer uptake in areas of locoregional recurrent and distant metastatic adenoid cystic carcinoma and expression was confirmed immunohistochemically. Adenoid cystic carcinoma is the most common malignant secretory gland tumor in the head and neck region.

According to several recent studies, PSMA PET may has a promising role in diagnostic imaging and radioligand therapy for recurrent and metastatic salivary gland cancers. However, the overall small number of studies comprising mainly case reports and retrospective studies may limit its interpretation and use in real-world settings currently, highlighting the unmet need for more comprehensive prospective studies.
Pheochromocytomas/paragangliomas overexpress somatostatin receptors, and recent studies have already shown [^{68}Ga]-DOTATATE PET/CT identified more lesions than other imaging modalities. With the increasing availability and use of DOTA analogs in the therapy of neuroendocrine tumors, we expect that [^{68}Ga]-DOTATATE PET/CT will become the preferred functional imaging modality for head and neck paragangliomas (HNPGLs) in the near future.

Key points

• [^{18}F]FDG PET/CT is highly effective for initial pretreatment staging of head and neck cancers, with greater sensitivity and specificity than CT and MRI.

• NCCN guidelines recommend [^{18}F]FDG PET/CT for initial staging of several types of head and neck cancers.

• [^{18}F]FDG PET/CT can modify radiotherapy planning in a significant number of patients with head and neck cancers.

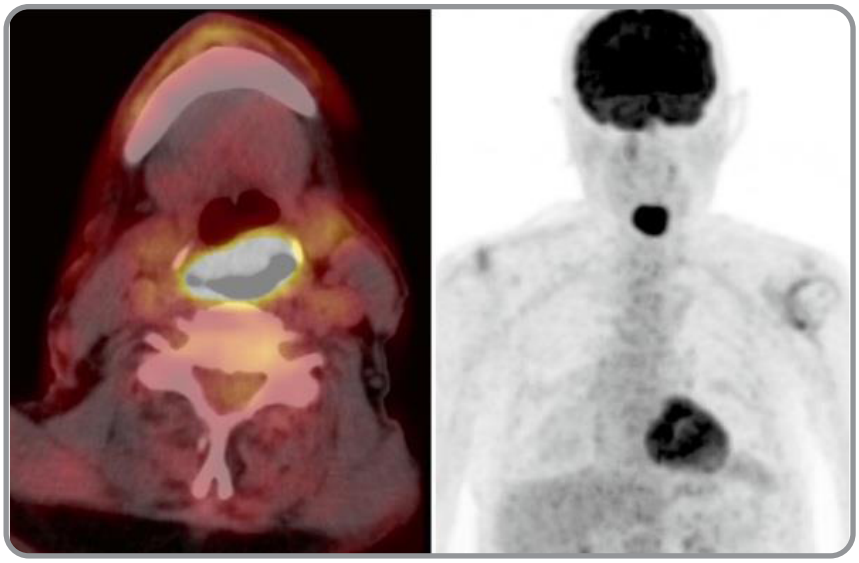
• [^{18}F]FDG PET/CT is more effective than CT or MRI for assessing response to therapy in head and neck cancer patients.

• [^{18}F]FDG PET/CT has greater sensitivity and negative predictive value than conventional imaging during post-therapy follow-up.

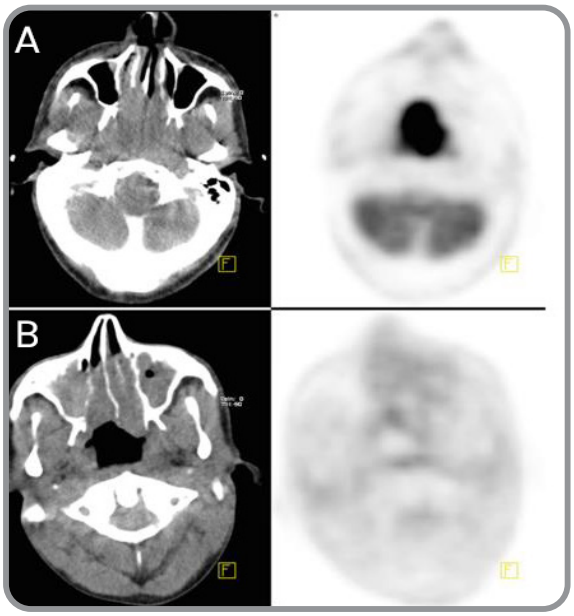
• [^{18}F]FDG PET/CT is more effective than CT or combined CT and MRI for detecting occult primary tumors in the head and neck region.

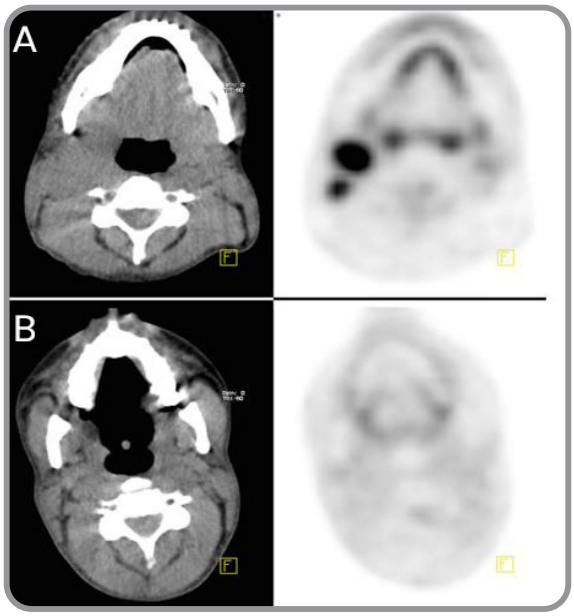
Case Presentations

Case 1: A 75-year-old female with newly diagnosed SCC of the epiglottis underwent [^{18}F]FDG PET/CT scan for primary staging. Scan shows primary malignancy at epiglottis without any lymph node involvement and distant metastasis.

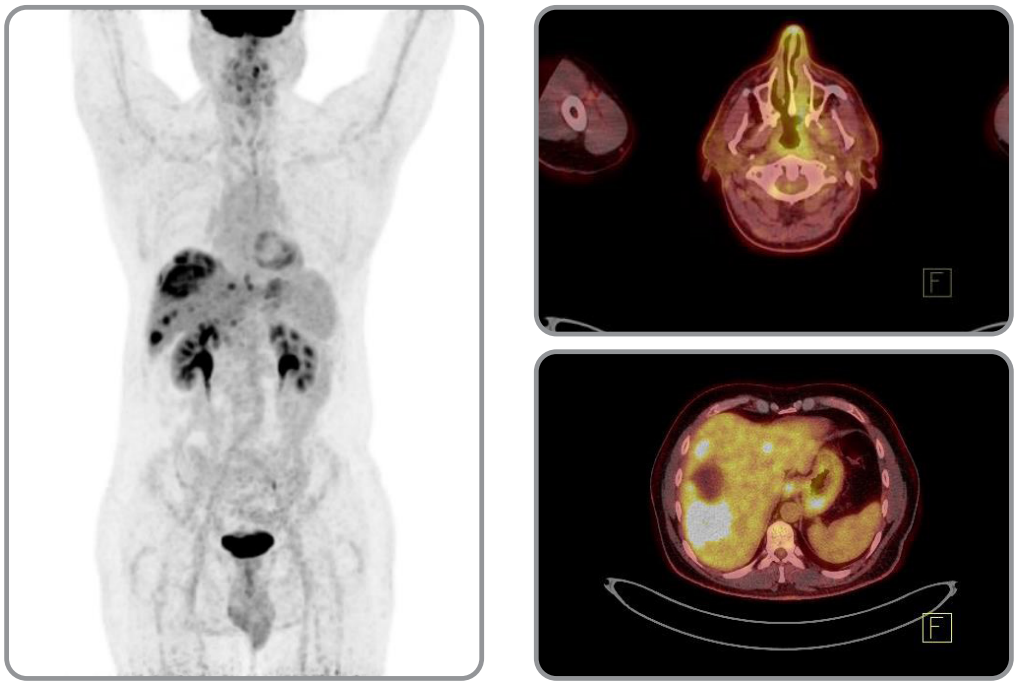


Case 2: A 34-year-old male with nasopharyngeal carcinoma was evaluated with [^{18}F]FDG PET/CT before and after having chemotherapy and radiotherapy for primary staging and therapy response, respectively. Intensely hypermetabolic mass lesion at nasopharynx was consistent with nasopharyngeal carcinoma along with two intensely hypermetabolic right cervical level II metastatic lymph nodes (a). All of the mentioned lesions are resolved after treatment indicating complete metabolic response to therapy (b).

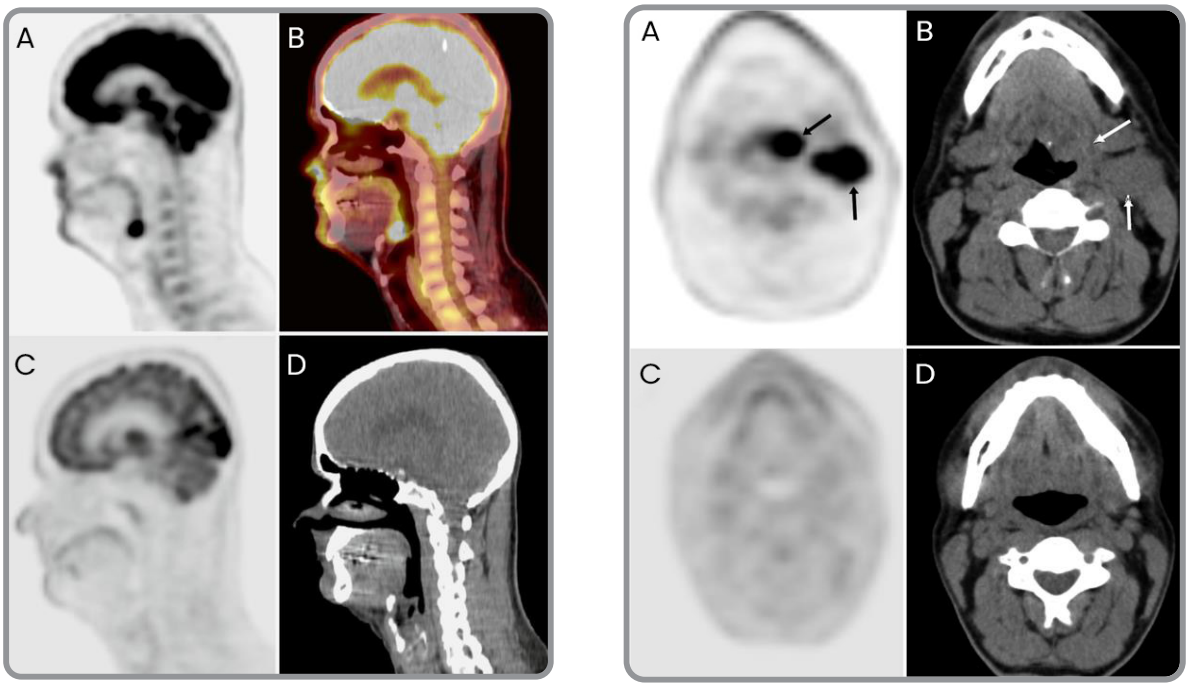




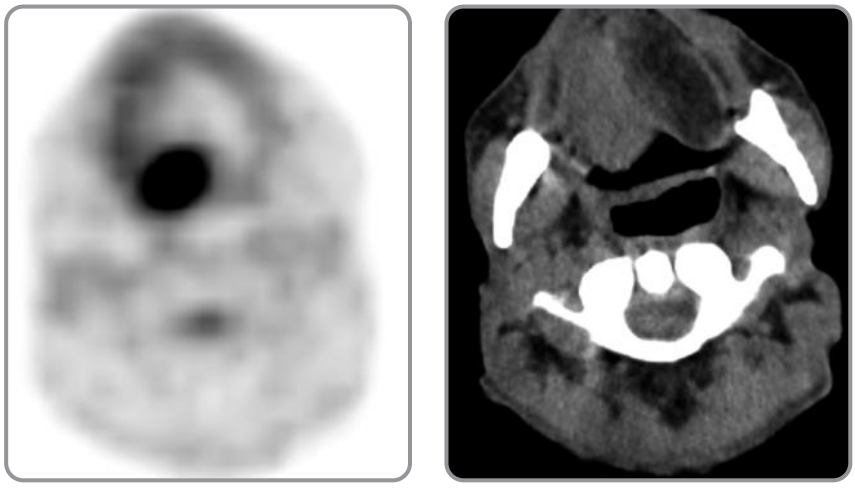
Case 3: A 41 year old male with nasopharyngeal cancer, status post chemoradiation therapy completed two years ago, referred for suspicious recurrence. Development of three [^{18}F]FDG avid right liver lobe hypoattenuating masses with central necrosis as well as few [^{18}F]FDG avid upper abdominal metastatic lymph nodes are evident.



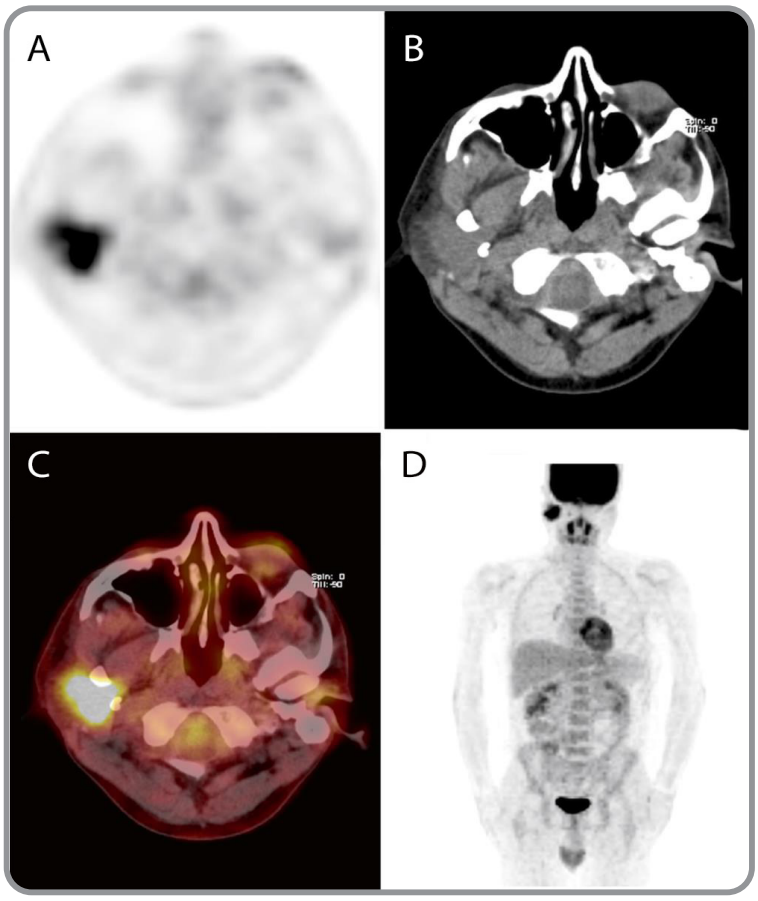
Case 4: A 50-year-old male was diagnosed with SCC of the left neck without identifiable primary lesion. Patient underwent [^{18}F]FDG PET/CT study for the detection of occult primary lesion (a, b). [^{18}F]FDG PET/CT study was repeated 3 months after the completion of the chemotherapy (c,d). Intense [^{18}F]FDG uptake at left base of the tongue consistent with the primary malignant lesion and hypermetabolic lesions at left upper cervical jugular area representing lymph nodes with metastatic involvement. [^{18}F]FDG PET/CT images after therapy show clearance of the pathological [^{18}F]FDG Uptake (c, d).



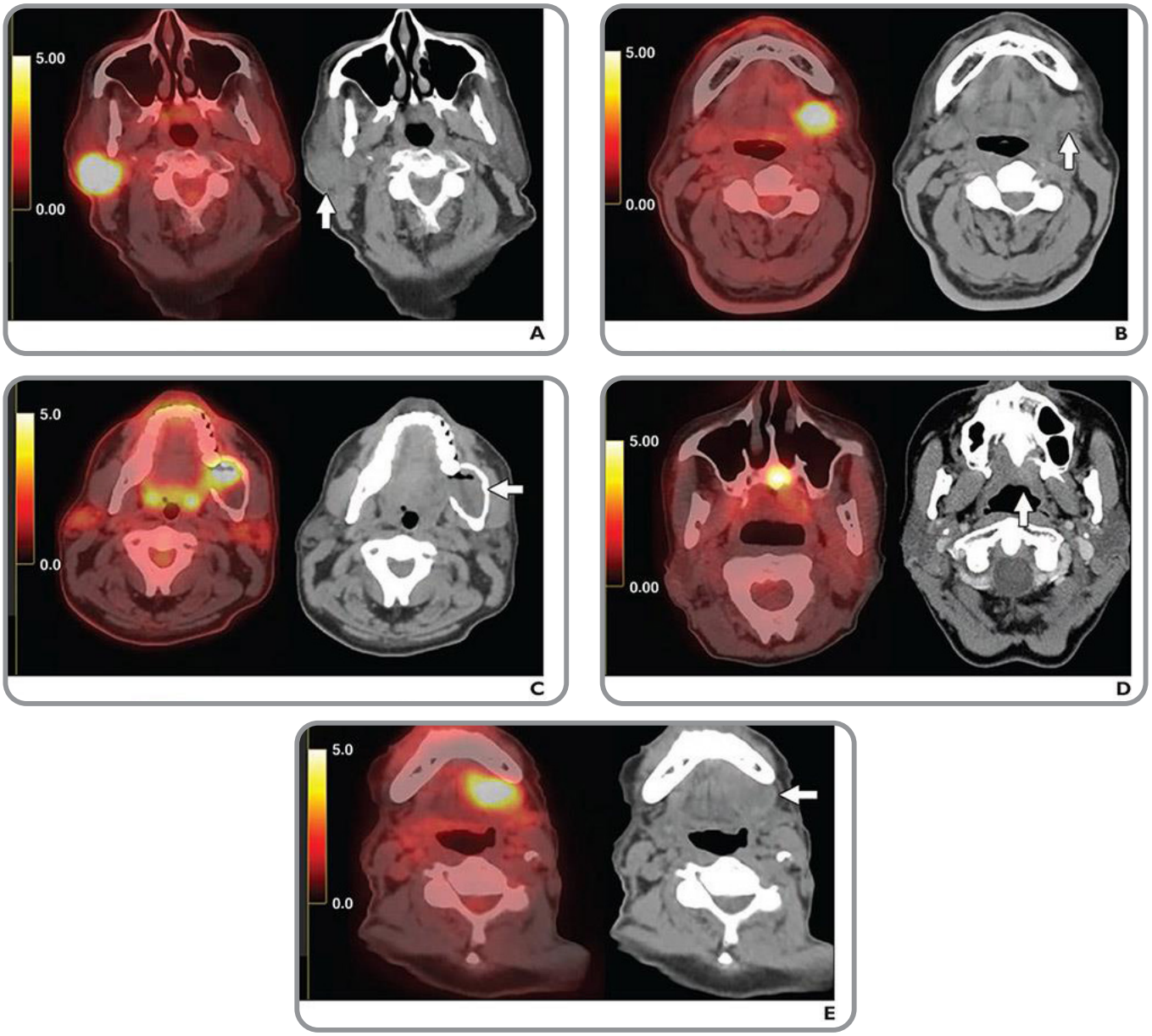
Case 5: A 55-year-old male underwent resection of tongue for tongue carcinoma and after surgery had a flap reconstruction of the tongue. The patient was referred for restaging purpose and a [^{18}F]FDG PET/CT study was performed. Extensive [^{18}F]FDG uptake at the posteromedial border of the flap compatible with recurrence of the primary malignancy.



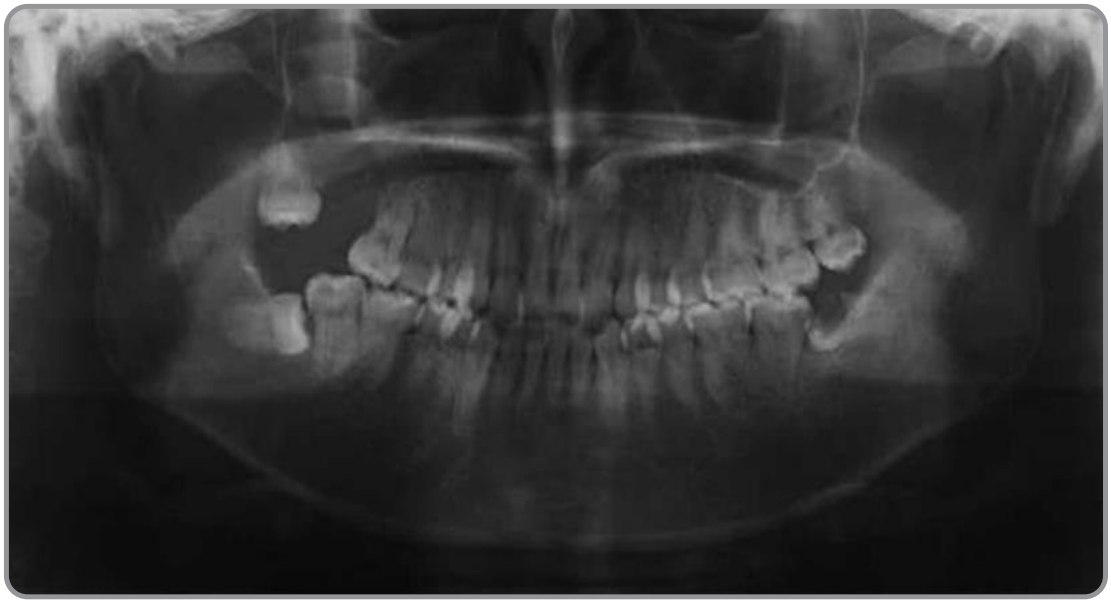
Case 6: A 45-year-old female was diagnosed as oncocytic carcinoma of the right parotid gland and underwent [^{18}F]FDG PET/CT for staging. PET/CT study showed intensely increased [^{18}F]FDG uptake at right parotid gland mass confirming the malignant nature of the lesion.



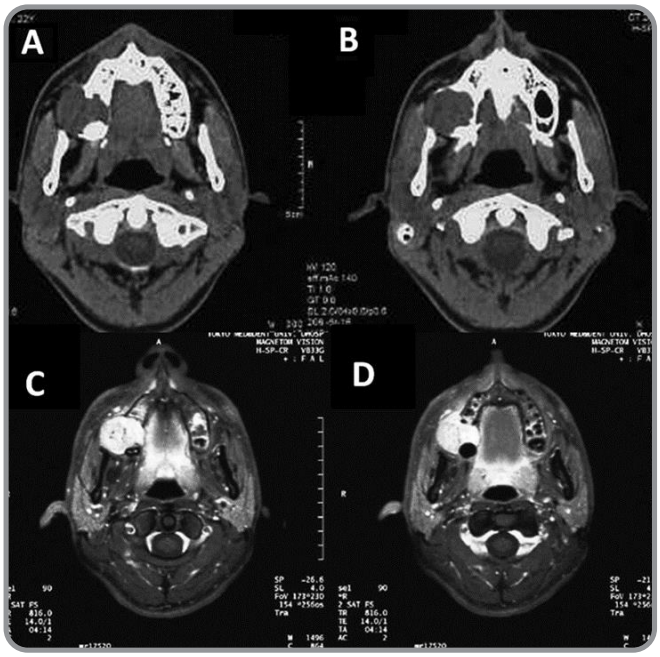
Case 7: Examples of salivary gland cancer. A–E, Axial [^{18}F]FDG PET/CT (left image in each panel) and CT (right image in each panel) images show salivary duct carcinoma (arrow, A) in right parotid gland, adenoid cystic carcinoma (arrow, B) in left submandibular gland, mucoepidermoid carcinoma (arrow, C) in left mandible, polymorphous adenocarcinoma (arrow, D) in soft plate, and epithelial-myoepithelial carcinoma (arrow, E) in left sublingual gland. SUV_{max} of these tumors were 16.7, 6.8, 6.6, 4.9, and 4.5 in A–E, respectively. All lesions were primary malignant tumors.



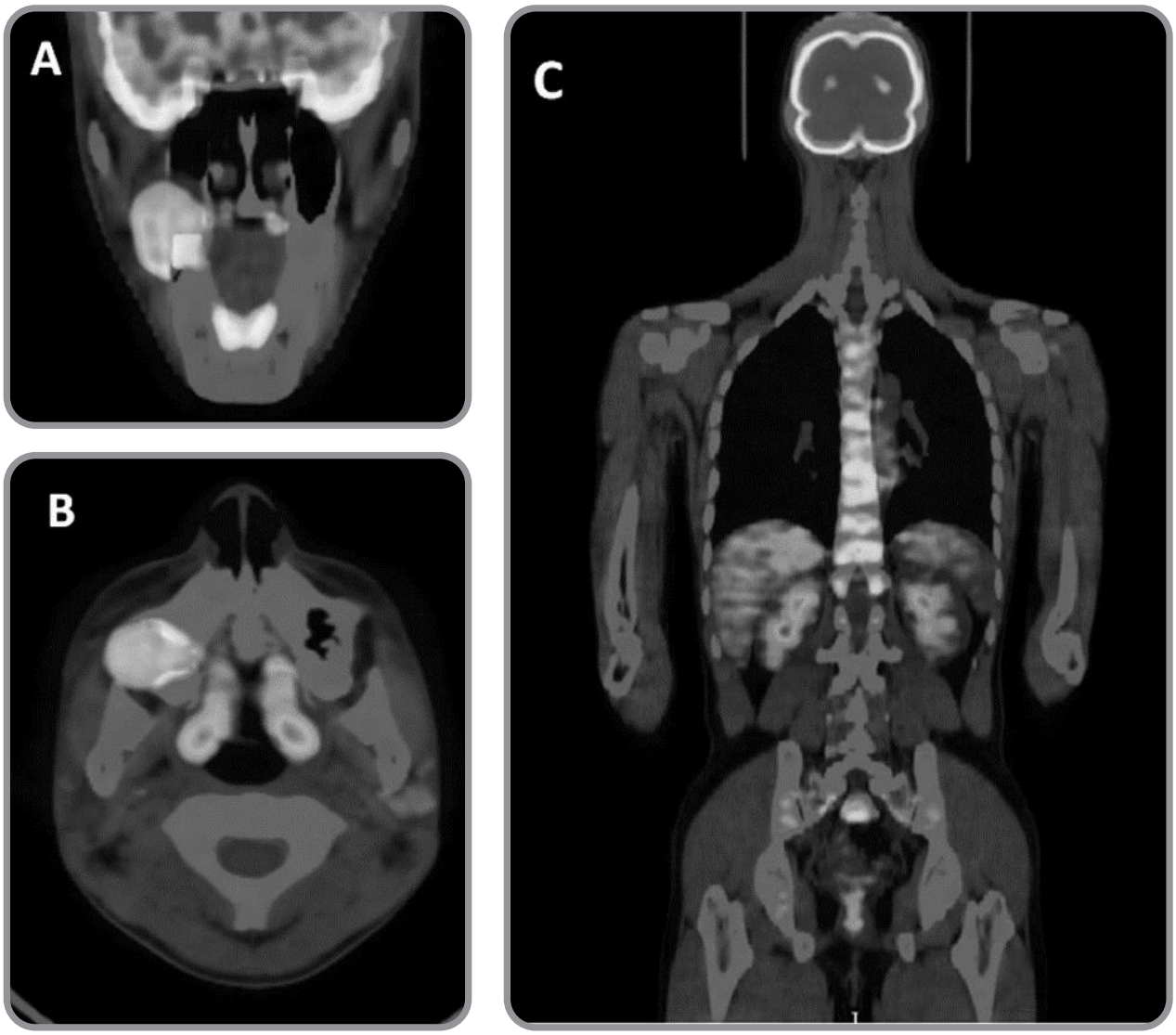
Case 8: A 22-year-old male was referred to the Department of Oral and Maxillofacial Surgery. The patient complained of painless swelling in the right maxilla that had been present for one month.
Panoramic radiography revealed a cystic radiolucent lesion in the right maxilla elevating the floor of the right maxillary sinus.



The axial CT image revealed a globular-shaped lesion arising from the inside of the maxillary bone, with destruction of the posterior wall and alveolar bone. The diameter of this lesion reached 30 mm in size. The right maxillary tuberosity and pterygoid plates appeared to be intact, but coronal CT imaging revealed destruction of the elevated sinus floor in the right posterior maxilla.

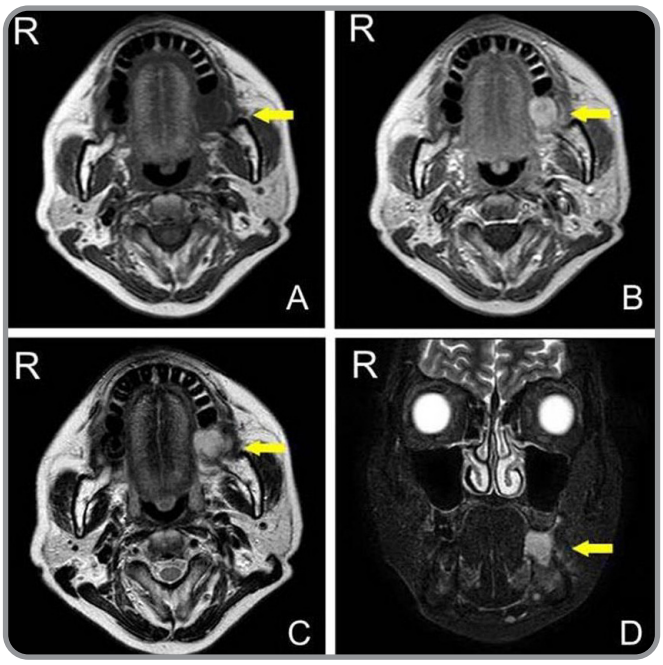


An incision biopsy was performed and the lesion was revealed not to be cystic, but to be a solid mass. Although the biopsy revealed that the lesion was an odontogenic carcinoma, its histopathological type was unidentifiable.
Next, [^{18}F]FDG PET/CT was performed to examine the extent of the primary lesion and the presence of regional lymph node and distant metastasis.

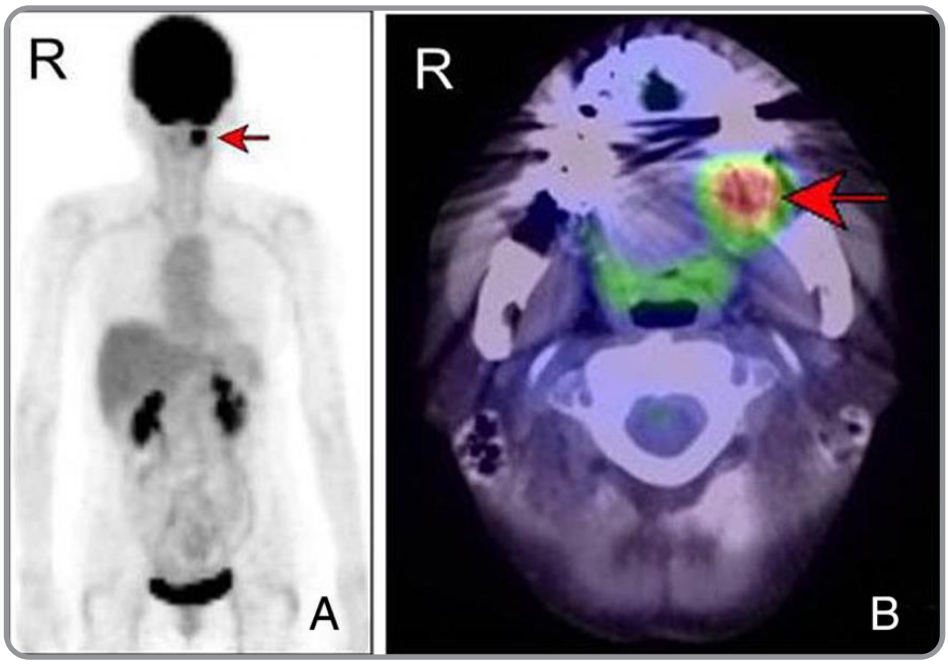


(A) coronal and (B) axial [^{18}F]FDG PET/CT images revealing a slight [^{18}F]FDG uptake in the primary tumor of the right maxilla and bilateral superior internal jugular lymph nodes. (C) No abnormal uptake, which would indicate distant metastasis, was observed on PET images.

Case 9: A 52-year-old woman was referred to the Department of Oral and Maxillofacial surgery for diagnosis and treatment of a mass on the left mandible.



A)T1-weighted axial image showing a mass of iso-intensity on the mandible (arrow). (B) Gadolinium enhanced T1-weighted axial image showing a highly and heterogeneously enhanced mass (arrow). (C) T2-weighted axial image showing high signal intensity within the mass (arrow). (D) Short-tau inversion recovery images showing high signal intensity in the mass (arrow).

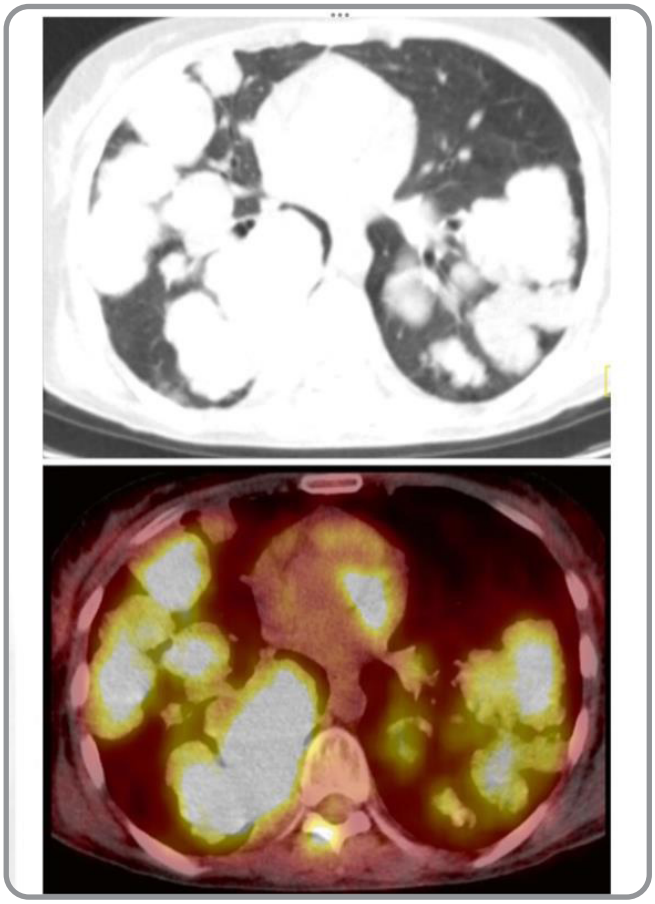


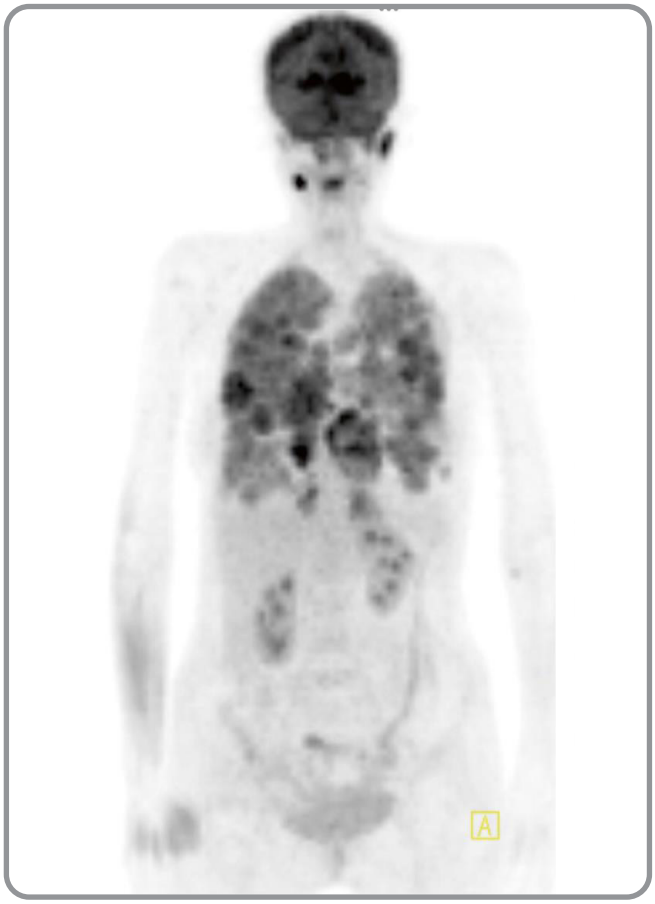
(A) [^{18}F]FDG PET/CT coronal image of the mass. There is an abnormal accumulation of [^{18}F]FDG in the left mandibular region (arrow). (B) PET/CT fusion image showing abnormal [^{18}F]FDG accumulation corresponding to the mass on the left mandible (arrow).
Pathological examination was consistent with the diagnosis of myofibroma.

Adenoid Cystic Carcinoma of Lacrimal Gland

Case 10 : A 42-year-old female is known case of adenoid cystic carcinoma of lacrimal gland.

MIP image shows intense and widespread [^{18}F]FDG uptake at both lung, compatible with metastatic lesions. Axial slices of CT and fusion images show mass lesions at both lungs with intense [^{18}F]FDG uptake.





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