Squamous Cell Carcinoma: PET/CT and PET/MRI of the Pre-Treatment and Post-Treatment Neck

Katie Suzanne Traylor, DO[1], Nicholas Koontz, MD[2], Kristine Mosier, DMD, Ph.D.[2]

[1]University of Pittsburgh
200 Lothrop Street, South Tower
Department of Radiology
2nd Floor, Suite 200
Pittsburgh, PA 15213
United States
traylorks@upmc.edu

[2]Indiana University School of Medicine
Department of Radiology and Imaging Sciences
Goodman Hall
355 West 16th Street, Ste. 4100
Indianapolis, IN 46202

Corresponding Author: Katie Suzanne Traylor, DO

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Abstract:

The incidence of head and neck cancer continues to rise annually, most commonly squamous cell carcinoma (SCCa). Advances in imaging techniques have improved diagnostic accuracy with important ramifications for initial staging and post-treatment surveillance. FDG-PET/CT and, more recently, FDG-PET/MRI have revolutionized the staging and surveillance of head & neck SCCa. We detail the diagnostic role of FDG-PET/CT and FDG-PET/MRI of SCCa at the different head and neck subsites, highlighting their role in identifying the primary tumor extent, regional nodal metastases, and distant metastatic disease in the pre-treatment and post-treatment setting, as well as implications for staging, treatment, and prognosis.

Key Words:

Squamous cell carcinoma, Head and Neck, FDG, PET/CT, PET/MRI, Staging, Prognosis, Risk Factors, Subsites

Introduction

Head and neck cancer is the sixth most common malignancy accounting for approximately 40,000 patients each year in the United States (US).[1, 2] Ninety-five percent of the head and neck cancers are histopathologically squamous cell carcinoma (SCCa) and found to arise from the mucosal surface of the oral cavity, oropharynx, hypopharynx, larynx, sinonasal cavity, and nasopharynx.[1] Locally advanced SCCa occurs in approximately two-thirds of patients with or without regional lymph node involvement.[3] Early-stage SCCa has a very favorable prognosis while more advanced disease has a poor prognosis and worse functional outcome.[4] Prognosis largely depends on the tumor type, histological variant, grade, and human papillomavirus (HPV) status. If all stages of head and neck cancer are considered, the 5-year survival is approximately 40-70%.[1, 5]

Currently, both CT and MRI are used to assess disease presence, tumor burden, and nodal involvement. Compared to CT, MRI offers superior soft tissue contrast resolution and demonstrates better sensitivity and specificity for differentiating whether a mass has adjacent soft tissue invasion, including perineural tumor spread.[7] While CT and MRI have similar success in detecting occult nodal metastasis, these modalities nevertheless show poorer sensitivity in determining involvement of nonenlarged lymph nodes relative to F18-fluoro-2-deoxyglucose (FDG) positron emission tomography (PET).[3]

In the United States, FDG-PET/CT has become commonplace during initial staging of head and neck SCCa, as well as during the post-

operative/treatment follow-up.[1, 5]. More recently, there has been the addition of PET/MRI, which combines the excellent soft tissue contrast resolution of MRI with the metabolic sensitivity of PET.[7] PET/CT or PET/MRI combines both diagnostic and functional imaging to aid in the detection of the primary tumor and potential metastatic foci locally and distantly.[8]

FDG-PET is a critical tool in oncologic imaging due to its ability to determine abnormally elevated levels of aerobic glycolysis in cancer cells.[5] The degree of FDG uptake in tissue is measured as the Standardized Uptake Value (SUV), which is a semi-quantitative value of the normalized concentration of radioactivity present within a lesion that is used to determine the glucose metabolism of the tumor. Thus, there is a well-studied association between FDG uptake in a tumor and the tumor burden. The SUV and volumetric parameters of PET/CT have been found to indirectly measure the expression of various markers of tumor aggressiveness. Moreover, multiple studies have shown correlation of the SUV_{max} with tumor stage, size and tumor dedifferentiation.[1] Pretherapy biomarkers such as elevated SUV_{max}, metabolic tumor volume, and total lesion glycolysis portends a poor prognosis.[6]

PET/CT is used to determine the presence of locoregional invasion, lymph node involvement and metastatic disease, and is implemented for staging, as well as surgical, radiation, and chemotherapy planning. In the post-treatment setting, PET/CT is employed to assess therapy response and to identify residual or recurrent disease.[1] PET/MRI has the potential to improve diagnostic accuracy where soft tissue contrast resolution is limited on CT or where CT

yields artifacts.[7] Additionally, given the etiology of most head and neck cancers, it is prudent to recognize that patients with head and neck SCCa have a higher prevalence of synchronous and metachronous primary tumors for which PET/CT and PET/MRI evaluation improves detection. [6]

Head and neck SCCa has a relatively low rate of distant metastatic disease (2-18%); however when it is present, there is a much poorer prognosis. The most common locations for metastatic disease from the head and neck are the lung followed by liver and bone. PET/CT evaluation for distant metastatic disease is important for proper treatment planning as the negative predictive value (NPV) for distant metastatic disease on PET/CT is 99%.[5]

Early stage disease in the head and neck is primarily treated surgically, which can result in a significant impact on quality of life due to impaired swallowing, speech deficits, and cosmetic deformity.[5] At an advanced stage the patient may undergo concurrent platinum-based chemoradiotherapy followed by surgery or surgical resection of the primary tumor with neck dissection followed by adjuvant chemoradiation. Despite these curative attempts, tumor recurrence remains common, and due to extensive posttreatment changes including edema, hyperemia, scarring, and loss of fascial planes, identification of recurrence remains challenging with imaging.[6] PET/CT is commonly used to assess initial treatment response due to the ability to detect viable tissue in the posttreatment neck. Despite the aggressive treatment options, many of these cancers unfortunately recur at the primary tumor site or locoregionally; therefore, these patients require continuous imaging surveillance. Kim et al have shown that PET

has a sensitivity of 86-100%, specificity of 43-97%, positive predictive value (PPV) of 42-71%, and a NPV of 98-100% in detecting persistent or recurrent disease after treatment. The PPV is low because PET/CT has a high false-positive rate due to post-treatment inflammation.[5]

Due to the post treatment inflammation, post treatment timing of the PET/CT to assess for tumor recurrence is critical. Timing is difficult to optimize, as it differs due to the extent of treatment and other patient-intrinsic factors. Detection of the earliest possible recurrence is necessary because recurrence greatly affects the outcome of salvage surgery.[9] The NPV is lower when the PET/CT is performed between 4 and 7 weeks post-treatment, while there is a higher NPV when the scan is delayed until 12 weeks after therapy. Goel et al determined that when the PET/CT was delayed 12 weeks or more after therapy, there was an improved sensitivity of 80% (versus 73%). Thus, the general consensus is PET/CT imaging should be delayed at least 12 weeks following treatment and this is the recommendation by the National Comprehensive Cancer Network (NCCN) clinical practice guidelines for head and neck carcinoma.[5,6]

Subsite-Specific PET/CT and PET/MRI Considerations

Nasal Cavity/Sinonasal

Sinonasal carcinomas are very rare and account for 3% of all head and neck cancers.[10] The major risk factors for developing sinonasal carcinomas include inhaled wood dust, chrome pigment, leather dust, isopropyl alcohol production, nickel, and radium 226 and 228 (and their decay products).[10] Exposures to these toxins are known to increase the risk of SCCa by 20 times.[11] According to the World Health Organization classification, there are 44 different histologic types of sinonasal malignancies, and the majority of these histologic types are of epithelial origin. There are 19 different epithelial malignancies, which includes the most common SCCa. Less common types include intestinal and non-intestinal type adenocarcinomas, salivary gland type carcinomas, and neuroendocrine tumors. SCCa itself accounts for 50-80% of all of the sinonasal malignancies and is most commonly found in 50-60 year-old males.[11]

Tumors of the nasal cavity are typically found at an advanced stage in 75-89% according to Lee et al because most of the symptoms that occur are very similar to the symptoms of chronic rhinosinusitis, resulting in delayed diagnosis. The prognosis markedly worsens if the maxillary sinus tumor invades posteriorly into the pterygomaxillary and infratemporal fossae versus when the tumor is confined to the anteroinferior portion of the sinus. Once the tumor invades these posterior structures, a simple en bloc surgical resection is difficult. Metastatic disease to the lymph nodes with sinonasal carcinomas occurs in approximately 7-15% according to Lee et al, and distant metastatic disease is quite rare. When local recurrence occurs after surgery, it most commonly occurs in the posterior

aspect of the maxillary sinus, periorbita, and the skull base. The 5-year survival rate with sinonasal SCCa is around 50% while the recurrence rate is approximately 56%.[12]

The imaging characteristics of SCC overlap with many other sinonasal malignancies, thus making it difficult or impossible to differentiate specific pathologies on imaging alone. On CT, SCCa typically presents as a heterogeneous solid mass with areas of central necrosis and irregularity with potential osseous destruction. Due to cellularity, a SCCa mass is often T2 hypointense on MRI, but may show areas of intrinsic T1 hyperintensity related to blood products, in addition to variable enhancement. On FDG PET/CT, sinonasal SCCa typically shows avid metabolic activity (Figures 1 and 2). However, these imaging findings are not specific to SCCa and can be found with other sinonasal malignancies, such as the less aggressive sinonasal adenocarcinoma. There are some differentiating imaging findings that can aid in suggesting a SCCa over adenocarcinoma, for example SCCa more commonly arises in the maxillary sinus antrum, enhances less, and have less well-defined margins.[11]

Sinonasal inverted papilloma (IP) is a common benign tumor of the sinonasal cavity and is known to be locally aggressive with a high rate of postoperative recurrence. According to Lee et al, IPs account for approximately 0.5-4% of all sinonasal tumors, and occasionally can harbor SCCa or undergo malignant transformation in approximately 9% of cases. Lee et al also stated that the 5-year survival rate for an IP is approximately 63% compared to 50% for sinonasal SCCa. It is difficult to differentiate a benign IP from an IP harboring

SCCa on routine MRI or CT imaging. Additionally, a biopsy sample may not identify the presence of SCC residing within the IP. It was initially thought that PET/CT may be of benefit in the identification of SCCa in an IP, but this has proven unreliable.[13] IPs have been found to have FDG uptake varying from minimal to marked (Figure 3). FDG-PET, however, may be useful when differentiating sinonasal IP from adjacent postoperative fibrosis and mucosal edema in suspected recurrent or residual IP.[14]

Nasopharynx

The nasopharynx includes the posterior choana, torus tubarius, Eustachian tubes, fossa of Rosenmüller, and the posterior pharyngeal wall. The superior-most boundary of the nasopharynx is the skull base and the inferior border is the soft palate.[15]

Nasopharyngeal carcinoma (NPC) is the leading cause of cancer deaths amongst the Cantonese population in Southern China and Hong Kong and rare in other parts of the world. There are three types of known NPC, including keratinzing SCCa (type I), non-keratinizing differentiated carcinoma (type II), and non-keratinizing undifferentiated carcinoma (type III). The undifferentiated carcinoma subtype is the most common, occurs in endemic areas, accounts for 93% of all of the NPC cases according to Mohandas et al, and are very commonly associated with Ebstein Barr virus infection. Differentiated carcinoma of the nasopharynx occurs in non-endemic areas, accounts for as many of 50%

of cases, and is associated with smoking and alcohol intake. SCCa of the nasopharynx is the rarest of all of the subtypes and has the worst prognosis. Radiation is the primary treatment of choice with localized disease, but chemotherapy is added in locally advanced cases.[16]

The American Joint Committee on Cancer (AJCC) has recently changed the T category of NPC. If there is involvement of the bony structures (paranasal sinuses, ptygeroid, skull base, vertebrae), the T category is now considered T3. Also, if the tumor involves the lateral or medial ptyergoid muscles or prevertebral muscles T category is considered T2, while it is considered T4 if there is extension of tumor beyond the lateral surface of the ptygeroid musculature or involvement of the parotid gland. These changes reflect a better prognosis if there is infiltration of the lateral ptygeroid muscle versus extension lateral to the muscle.[17]

MRI has been found to be an excellent imaging modality due to its excellent spatial resolution and soft tissue contrast in managing NPC, whereas, CT is more commonly used in initial staging and radiation planning. MRI demonstrates superior sensitivity at determining the extent of disease and whether there has been spread of the primary tumor into the parapharyngeal space, orbit, paranasal sinuses, and/or retropharyngeal adenopathy, which impacts staging and treatment planning.[16]

PET/CT has been found to be a valuable imaging modality in staging NPC, although it tends to underestimate tumor volume and extent at the nasopharynx, skull base, brain, cavernous sinuses, and orbits when compared to

MRI. Underestimation may be due to overall decreased FDG avidity in early disease, overall decreased resolution of PET/CT versus MRI, and high metabolic uptake of the adjacent brain, which may obscure adjacent tumor uptake (Figure 4). Due to the inability of PET/CT to resolve soft tissue details it is difficult to differentiate between tumor invasion versus tumor compression of the surrounding tissues.[16] However, FDG-PET/CT can detect small NPCs which are occult on both MRI and CT.[18] FDG-PET/CT has a sensitivity of 96%, specificity of 94%, PPV of 96% and NPV of 94% which is significantly higher than CT alone (71%, 76%, 80%, and 67%). PET/CT has been shown to result in downstaging of NPC in 17-23% of cases and upstaging in 8-10%.[16]

The presence of metastatic lymphadenopathy in the setting of NPC is associated with a poor prognosis. This is especially true in N3 category disease, where there is bulky (conglomerate) lymphadenopathy measuring > 6 cm, or lower neck (below the caudal border of the cricoid cartilage) metastatic lymph nodes. Also, Ai et al showed that there is a high propensity of NPC nodal disease to demonstrate extranodal extension (ENE), thought to occur in in 33.6-39.8% of cases. However, in contrast to the significant effect of ENE on locoregional control and overall survival for oropharyngeal carcinoma, this is different for NPC where patient survival/prognosis is largely dependent on a high total nodal volume and nodal necrosis.[19]

PET/CT has been found to have a high accuracy rate in assessing metastatic lymph nodes in NPC. When evaluating lymph nodes with diagnostic imaging such as MRI and CT, the assessment depends on morphology, size,

and enhancement. This may lead to missed pathological nonenlarged nodes harboring microscopic tumor cells PET/CT, on the other hand, has a sensitivity of 97-100% and a specificity of 73-97% in evaluating such nodal disease in NPC while MRI sensitivity and specificity is much lower (73-97%), according to Mohandas et al. PET/CT has been found to be more accurate with infrahyoid neck lymph nodes involvement, while retropharyngeal lymph nodes are more difficult to detect likely due to marked uptake from the adjacent NPC. However, the addition of intravenous contrast markedly improves retropharyngeal node detection.[16]

PET/CT has a very important role in the detection of distant metastatic disease, thus having a direct impact on treatment and prognosis. One study found that PET/CT changed the treatment in 33% of patients with NPC, related to both detection of nodal disease and metastatic disease not otherwise identified on other diagnostic imaging studies.[16]

PET/CT is the study of choice for post-treatment imaging in determining the presence of residual and recurrence of disease and differentiating it from post-radiation changes/inflammation (Figure 5). The sensitivity and specificity of post-treatment PET/CT in detecting residual/recurrence disease is 95% and 90% respectively, according to Mohandas et al. When a NPC is first diagnosed as a T4 category, it has been found that PET/CT has a much higher specificity for recurrence when compared to MRI (96% versus 63%). The new development of PET/MRI has the potential to even be better than PET/CT and MRI alone,

PET/MRI can better delineate the detail with intracranial spread, retropharyngeal lymphadenopathy, and perineural tumor spread (PTNS).[16]

Oropharynx

The oropharynx includes the base of tongue, soft palate/uvula, posterior wall of the pharynx, valleculae, palatine/lingual tonsils, and anterior/posterior tonsillar pillars.[15]

Many head and neck SCCa have a high association with alcohol and tobacco use. More recently, human papilloma virus (HPV) infection (most commonly HPV type 16) has been found to be a major etiology of oropharyngeal SCCa, and in the United States, HPV-related SCCa accounts for approximately 70% prevalence among oropharyngeal HPV. Relative to traditional demographics of non-HPV SCCa, HPV SCCa occurs in a younger patient population, most commonly white males, and is strongly associated with high risk sexual behavior.[20] HPV positive oropharyngeal tumors can be detected via immunohistochemistry for p16 kinase inhibitor, which is important for stratifying management as these tumors respond better to chemotherapy, radiation, and chemoradiation therapies resulting in a better prognosis then HPV negative SCCa of the oropharynx. Also, HPV positive tumors tend to need less frequent imaging surveillance.[6] Most commonly p16 positive tumors present with multiple, bulky, bilateral lymphadenopathy with a much better survival than their p16 negative counterparts with the same imaging findings.[17]

The presence of nodal disease continues to be an important prognostic factor, according to Goel et al, with rates of survival decreasing by 40-50% with the presence of metastatic cervical lymph nodes. The major advantage of PET/CT is detecting metabolically active lymph nodes which are clinically occult, nonenlarged on MRI or CT imaging, and otherwise would have not been detected (Figure 6). Even in suspected N0 neck disease, there remains a 20-30% chance of occult nodal disease; therefore, these patients typically undergo an elective neck dissection in order to accurately stage the patient.[6]

In the posttreatment setting of oral cavity and oropharyngeal cancer, the imaging modalities which influence clinical decisions are CT, MRI and PET/CT. Additionally, per the NCCN, regular clinical examinations remain imperative in post-treatment follow-up.[9] PET/CT is an accurate and sensitive imaging modality for post-treatment evaluation of patients with oropharyngeal SCCa over CT alone.[20] PET/CT is very important in detecting residual or recurrent disease, as early detection of recurrence is extremely important in the potential usage of salvage neck surgeries (Figure 6).

There are persistent challenges that radiologists face when reading posttreatment PET/CT studies. First, the optimal time interval for the initial post treatment evaluation is 12 weeks. Acquiring PET images prior to 12 weeks can result in false negatives and some false positives due to postsurgical fibrosis, edema, and inflammation. Moreover, loss of symmetry and normal fascial boundaries from treatment changes may obscure tumor recurrence or may make identification of recurrent disease more challenging. In order to be the most

helpful to the clinician in these cases, the radiologist must have a firm understanding of the anatomy and be able to identify potential involved subsites, as these areas affect the patient's treatment. These subsites include the posterior oropharyngeal wall, palatine tonsils/tonsillar pillars, base of tongue, and the soft palate/uvula.[9] On occasion, the tumor may be masked due to the adjacent, normal, physiologic uptake of the pharyngeal lymphoid tissues. Also, false-positive results are more likely to occur in locations prone to inflammatory processes such as the palatine tonsils and Walderyer ring of lymphoid tissue. Most of these difficulties with PET/CT can be overcome with the addition of a diagnostic post-contrast CT of the neck.[6, 18]

Oral Cavity

The oral cavity includes the hard palate, retromolar trigone, anterior two-thirds of the tongue, floor of the mouth, maxillary/mandibular alveolar ridges, teeth and gingiva, bucca mucosa, and lips. Tumor involvement of these subsites can drastically affect the patient's treatment plan and need to be assessed on imaging.[9,15]

The oral cavity is often difficult to assess on CT due to substantial artifacts from dental restorations or appliances and MRI, PET/CT, or PET/MRI may be of benefit (Figure 7). PET/CT has been found to more accurately characterize the primary tumor. MRI does not experience the same artifacts as CT; however, MRI is more sensitive to patient motion artifacts.[6, 18] Mandibular involvement is

extremely important in surgical planning, and the diagnostic CT portion of the PET/CT highly aids in the determination of osseous involvement with a high sensitivity (83-96%) and variable specificity (53-92%), according to Goel et al. Goel et al also determined that PET/CT has a sensitivity of 100% and specificity of 85% when it comes to mandibular tumor involvement. Therefore, PET/CT can aid in accurate primary tumor staging and help with radiotherapy and surgical planning.[6]

In the recent AJCC Cancer Staging Manual, 8th Edition, the staging of oral cavity carcinomas was updated to remove the previously-included extrinsic tongue muscles involvement. Although removed due to lack of prognostic value of this finding, invasion of the extrinsic tongue muscles remains important for surgical planning and reconstruction purposes. The depth of invasion (DOI) of the tumor was recently added to the staging criteria; however, this is a pathology finding rather than an imaging finding and is believed to be most consistent with tumor thickness on imaging. The tumor thickness on imaging includes the endophytic and or exophytic components of the tumor, thus tends to over or underestimate what the pathologist measures to be the true DOI. PET/CT has been found to have high accuracy in the detection of primary tumor (Figure 7), however, due to poor spatial resolution there is PET/CT may be lacking in the determination of tumor extent into neighboring soft tissues, an area where PET/MRI theoretically offers superior advantage.[6, 18]

In oral cavity SCCa, the presence of lymph node micrometastases remain a challenge on imaging. The surgeon often elects to complete a neck dissection

in these patients for early oral cavity carcinomas, as it is challenging to reliably identify occult lymph node micrometastases, particularly if the interpreting radiologist relies too heavily on lymph node size as a screening tool for detecting nodal metastases. Nevertheless, Weiss et al. found the presence of occult metastatic lymph nodes in stage N0 neck cancer occurs in less than 20% of cases, and given this data watchful waiting may be considered. Both MRI and PET have been found to have NPVs of greater than 80% for occult metastatic nodes.[5] When the clinician has a negative neck physical examination in a patient with oral cavity SCCa, PET-CT can aid the other diagnostic imaging in determining PET avid, suspicious non-enlarged lymph nodes. This is particularly helpful in T1-T3 oral cavity SCCa. (Figure 7).[3]

Larynx

The larynx is subdivided into the supraglottic, glottic, and subglottic larynx. The supraglottic larynx is the origin site of laryngeal SCCa in approximately 30% of cases, which may include involvement of the suprahyoid free portion of the epiglottis, the infrahyoid fixed portion of epiglottis (petiole), the aryepiglottic folds, arytenoids, false vocal folds, laryngeal ventricle, preepiglottic fat, and paraglottic space.[15] The glottic larynx is the site origin of laryngeal SCCa in approximately 65% of cases, which may involve the true vocal folds, anterior commissure, and posterior commissure.[15] The subglottic larynx extends inferiorly below the true vocal folds and terminates above the first tracheal ring. It is uncommon for SCCa

to primarily originate within the subglottic, although involvement of the subglottic larynx is much more commonly seen with transglottic extension of tumor.[15]

Over the years, due to improved surgical techniques patients have had a better quality of life; however, despite this fact, the overall survival has not improved greatly due to advanced stage at time diagnosis. Most of the causes of death are due to locoregional recurrences and distant metastatic disease. Due to post-surgical/treatment changes after surgery, it is challenging to assess for locoregional recurrence on MRI and CT due to changes in anatomy, scar/fibrotic tissue, and loss of tissue-fat planes. It is, however, extremely important to be able to detect recurrences, as salvage treatment is less successful once the disease reaches a more advanced stage. PET/CT is highly reliable in the diagnosis of recurrent laryngeal malignancy and lymph node disease with a sensitivity of 100%, a specificity of 88%, and an accuracy of 93.3%.[21]

When the tumor invades the preepiglottic fat and the paraglottic space, there is an increased risk for nodal metastatic disease due to the rich lymphatics. These tumors also tend to have a higher recurrence rate and worse outcome when there is invasion of the thyroid/cricoid cartilages and especially when there is full thickness cartilage invasion (Figure 8). The role of MRI and PET/MRI in assessment of laryngeal SCCa is not as well established but may be considered for trouble shooting indeterminate CT findings, including assessment of cartilage invasion and paraglottic extension of laryngeal tumor. Although pretreatment PET/CT is excellent as a baseline study, subsequent PET/CTs without contrast yields no more information than MRI and CT.[18]

Hypopharynx

The hypopharynx includes the posterior cricoid pharyngeal mucosa, posterior pharyngeal wall, and pyriform sinuses. The superior-most aspect of the hyopharynx is at the level of the hyoid bone at the pyriform aperture and the inferior-most aspect of the hypopharynx is the lower border of the cricoid cartilage.[15]

SCCa of the hyopharynx is typically diagnosed at an advanced stage and therefore, tends to have a poor prognosis, and more than 75% of patients are a stage III or IV at the time of initial diagnosis, according to Joo et al. Joo et al, also found that nodal disease is typically present in 60-80% of patients at the time of diagnosis; therefore, it is ideal to have an imaging modality, such as PET/CT or PET/MRI, that will assess local and distant disease. Hypopharyngeal carcinoma has a high propensity of involving the local lymph nodes, thus making nodal staging crucial in the determination of tumor stage (Figure 9). Currently, the main imaging modalities consist of CT, MRI, and PET-CT with increased usage of CT and MRI as PET-CT often has erroneous uptake from movement during the exam.[22]

Lymph nodes

The presence of metastatic lymph nodes in head and neck SCCa is one of the most important factors in predicting patient prognosis; therefore, the patient's otolaryngologist or oncologist must also consider lymph node treatment even if metastatic disease is not evident clinically. The presence and extent of lymph node disease also helps the surgeon plan for the type of neck dissection or for the radiation oncologist to plan the radiation fields. This preoperative surgical planning helps decrease duration of the operation and ensures sufficient coverage of involved lymphatics.[3]

In order to identify an abnormal lymph node, the lymph node size and the morphologic characteristics must be assessed on imaging. On non-PET imaging, a rounded shape, loss of normal fatty hilum, focal cortical thickening, focal nodal inhomogeneity, and cystic change (necrosis) are abnormal and suspicious for nodal metastases regardless of lymph node size.[17] ENE also significantly increases the likelihood for locoregional recurrence and distant metastatic disease resulting in a worse prognosis.[3, 22] The presence of ENE, however, is not included in the staging of HPV positive SCCa of the oropharynx as it has been found to not have a significant impact on prognosis.[17] The main imaging modalities for assessment of the presence of ENE are CT and MRI; however, surgical removal and pathological assessment remain the most reliable.[22] On imaging, ENE can be suggested when there is clear infiltration of perinodal tumor beyond the lymph node into the surrounding soft tissues.[17]

Even though MRI is very often helpful in head and neck SCCa, it has been found to have a slightly disappointing sensitivity and specificity when it comes to

detecting metastatic nonenlarged lymph nodes. The detection of nodal disease on imaging largely depends on abnormal morphologic imaging criteria.[5, 7] Contrast-enhanced MRI has been found to have a sensitivity of 72% and a specificity of 88% in the detection of metastatic lymph nodes.[23]

PET/CT, on the other hand, has superior sensitivity in the detection of nodal disease when compared to PET, CT or MRI alone (Figure 10). The sensitivity of PET/CT is 92-100% with a mixed specificity of 77-93% in the detection of metastatic lymph nodes.[5] It has also been found that PET/CT yields a very high NPV (94.5-96%) in the surveillance of head and neck SCCa.[1-3, 8] Occult metastatic cervical lymph nodes have a 71-72% increased detection rate with the addition of PET/CT.[3]

The detection of nodal disease on PET/CT depends on technical factors, including the uptake time after radiotracer injection and the study duration for the dedicated neck portion of the PET/CT, as well as the burden of metastatic tumor within an involved lymph node and the presence or absence of nodal necrosis, which can result in false negative PET findings. Yamamoto et al. found that 8 minute imaging acquisition for the dedicated neck portion of the PET/CT yielded higher quality images rather than the typical 2-minute time frame. Additionally, with a longer imaging delay there is increased ability to detect small FDG positive lymph nodes. PET and MRI together yield a sensitivity of 85% and specificity of 92%, which is not much different than the individual studies.[5] Specific to PET/CT, Keski-Santti et al. report a 3-month post-treatment sensitivity of 59%,

specificity of 94%, PPV of 71%, and the NPV of 93% for the detection of metastatic lymph nodes.[5]

Perineural Spread

PNTS consists of tumor spreading along named nerves away from the primary tumor site, which is associated with a poorer clinical prognosis. Despite significant extension along nerves away from the primary site, the patient may be asymptomatic and PNTS is difficult to detect at the time of surgery. Traditionally, study of choice for PNTS detection is MRI due to high soft tissue contrast resolution; however, coupling the superior tissue contrast resolution of MRI with the metabolic activity of PET on hybrid PET/MRI systems may yield improved detection of PNTS (Figure 11).[18] PNTS is more difficult to identify on CT, but may on occasion be detected on PET/CT, manifesting as abnormal curvilinear hypermetabolic activity along the affected nerves.

Skin Cancers

Nonmelanoma skin cancer has consistently been on the rise with the second most common nonmelanoma skin cancer being SCCa.[24] SCCa accounts for 20% of all non-melanoma skin cancers and most commonly affects Caucasians.[25] More than half of these cutaneous SCCa arise from the head and neck. The current staging for nonmelanoma skin cancer includes the tumor

size and thickness, level of invasion (beyond the dermis), nodal status, and distant metastatic disease.

Currently, treatment in patients with nodal disease, but without distant metastatic disease consists of surgical resection of the primary tumor, neck dissection for cervical lymph node involvement, followed by regional post-operative radiation.[24, 26] SCCa involving the scalp, ear, and lip has been found to have a higher recurrence rate and are more likely to have nodal metastasis (Figure 12). It is critical to remember that intraparotid lymph nodes represent the first order nodal drainage basin for skin of the ear, portions of the scalp, and portions of the face. Other risk factors for nodal metastatic disease include prior radiotherapy and a large primary tumor. Skin SCCa demonstrates a high propensity of having perineural invasion, which is a strong predictor of loco-regional recurrence.[26] According to Supriya et al, approximately 5% of SCCa skin cancers metastasize to the regional lymph nodes; however, in more aggressive skin cancers, this may increase to 10-20%. Prior to surgical resection, the evaluation for the presence of lymph node metastasis is mandatory due to its associated poor prognosis and an approximate 40% survival at 5 years. Distant metastatic disease usually occurs in the setting of patients with regional lymph node disease, and these patients rarely survive beyond 2 years despite aggressive treatment.[26]

Patients with cutaneous SCCa have been staged utilizing CT or MRI; however, with the greater availability of PET-CT, its use in staging has increased.[26] PET-CT is well documented in the evaluation of primary SCCa

and staging in the head and neck; however, it is less well documented when it comes to cutaneous SCCa. It has been found the PET/CT has a high sensitivity of locating primary cutaneous SCCa (83.3%).[27] Despite the benefits of PET-CT with melanoma, the usage of PET-CT with cutaneous SCCa does not yield the same benefits. PET-CT in this clinical scenario has not been found to offer additional benefit over conventional CT and MRI imaging when staging the primary malignancy. Also, no change in management has been found with the addition of PET-CT.[26]

Conclusion

SCCa of the head and neck continues to be on the rise in the US. It is imperative at diagnosis to know the full extent of the primary tumor, locoregional lymph node involvement, and presence of distant metastatic disease; these findings have a direct impact on treatment and prognosis and are readily assessed with PET/CT or PET/MRI. Pre- and post-treatment PET imaging has also become a well-documented method for initial staging and post-treatment surveillance in patients with head and neck SCCa, although in some sites in the neck it has a higher benefit. Additionally, PET/CT and potentially PET/MRI are very helpful in identifying micrometastatic disease in nonenlarged lymph nodes when compared to CT and MRI alone.

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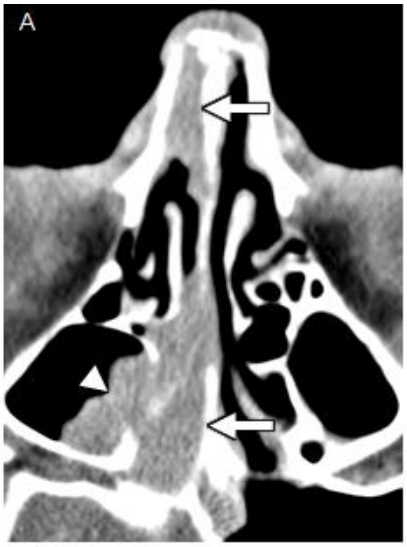
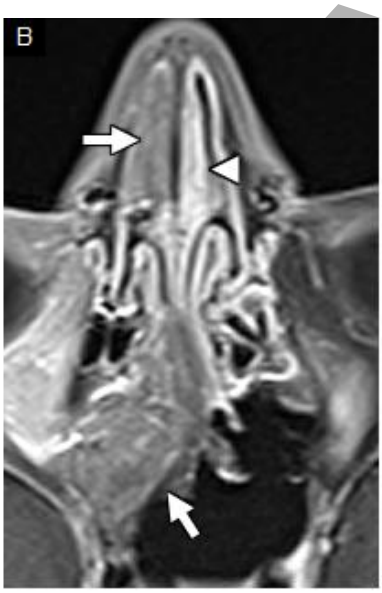
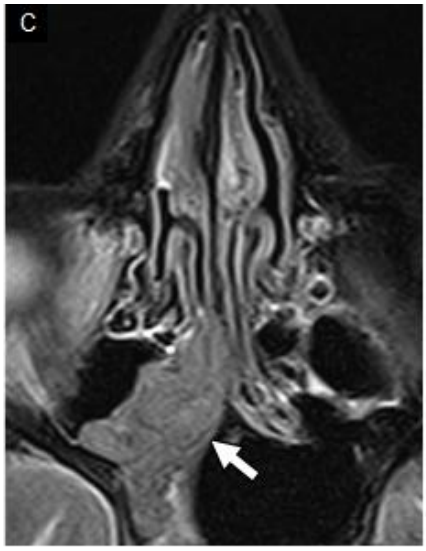
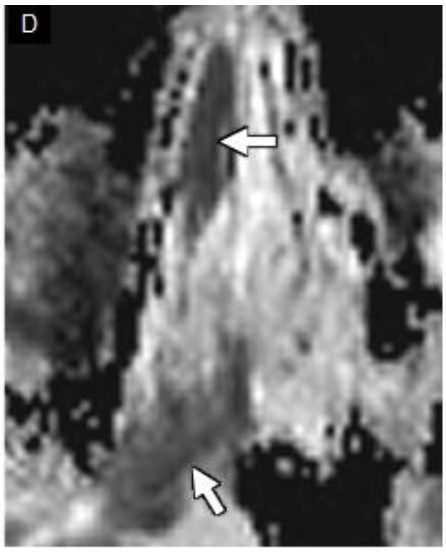
Figure Captions









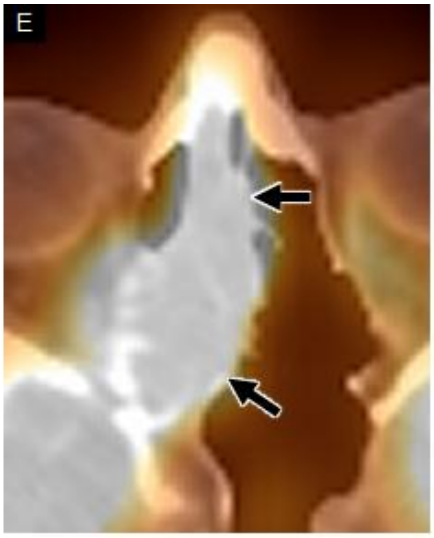
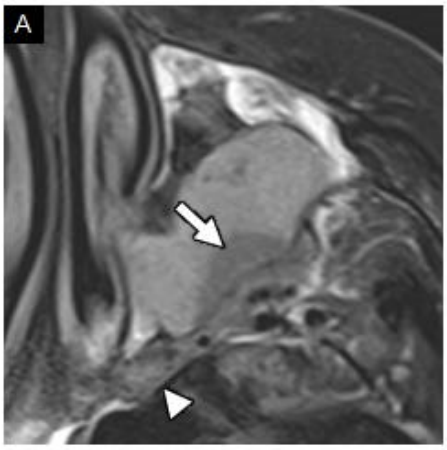
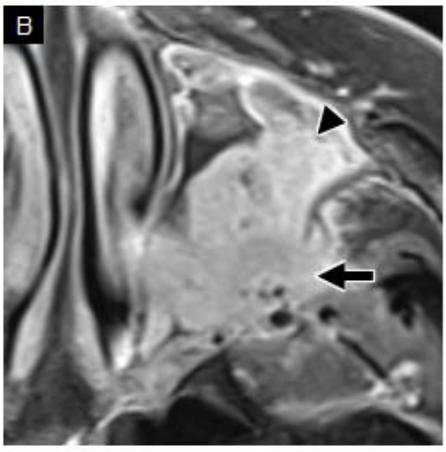
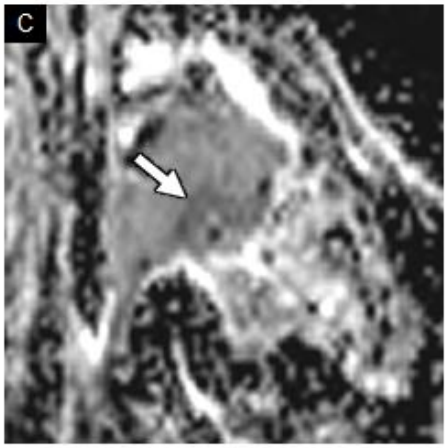
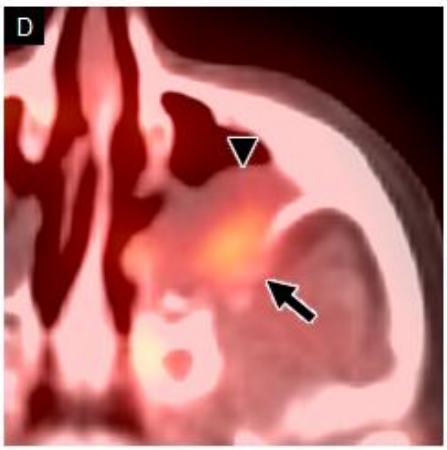


Figure 1. 72-year-old woodworker with T3N2cM0 high grade squamous cell carcinoma of the right nasal cavity. Axial CECT (A) shows a soft tissue mass (white arrows) centered within the right nasal cavity with extension into the superior right maxillary sinus (white arrowhead). Axial T1WI C+ FS MRI (B) demonstrates heterogeneous enhancement of the mass (white arrows), which enhances much less avidly than the normal sinonasal mucosa (white arrowhead). On axial T2WI FS MRI (C) and axial ADC map (D), the mass is hypointense (white arrows), indicative of a high cellularity tumor. Axial 18F-FDG PET/CT (E) shows markedly high FDG avidity of the right nasal cavity mass (black arrows).









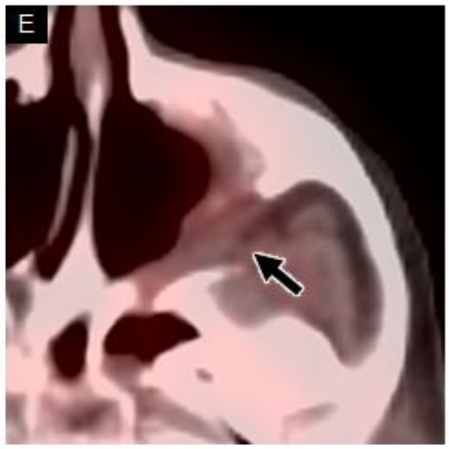
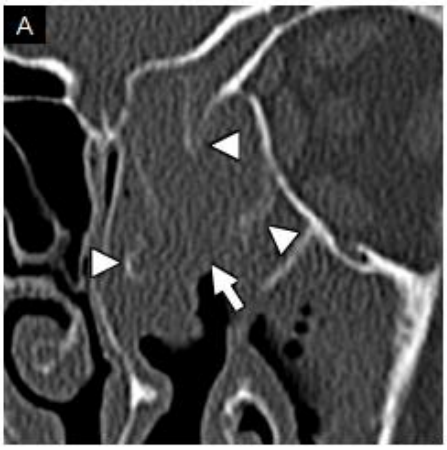
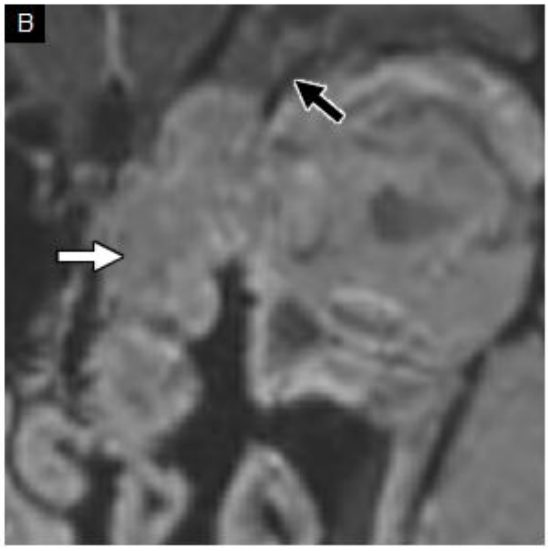
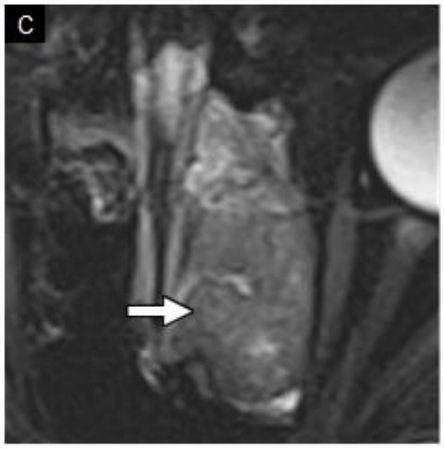


Figure 2. 85-year-old man with a pT4b nonkeratinizing, moderately differentiated squamous cell carcinoma of the left maxillary sinus. Axial T2WI FS MRI (A) shows a hypointense mass along the posterior wall of the left maxillary sinus (white arrow) with extension into the left pterygopalatine fossa (white arrowhead). Axial T1WI C+ FS MR (B) shows a homogeneously enhancing mass (black arrow), which enhances less avidly than the adjacent, thickened sinonasal mucosa (black arrowhead). Axial ADC map (C) shows the mass to be mildly hypointense (white arrow), which suggests a mildly hypercellular mass. Pretreatment axial 18F-FDG PET/CT (D) shows the mass to be mildly FDG avid (black arrow), as well as delineates the extent of the tumor relative to the adjacent non-FDG avid sinus mucosal disease (black arrowhead). Post-

treatment axial 18F-FDG PET/CT (E) shows no residual/recurrent hypermetabolic tumor in the maxillary sinus (black arrow).







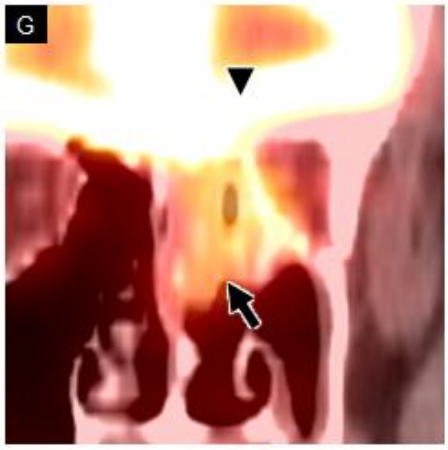
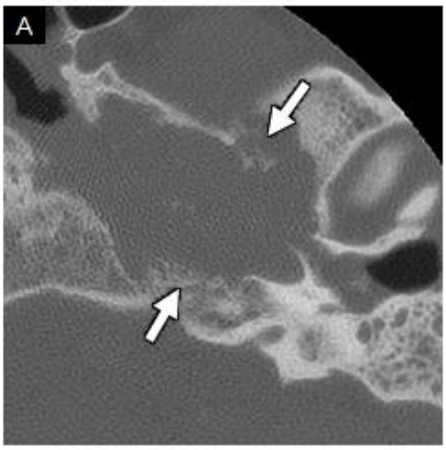
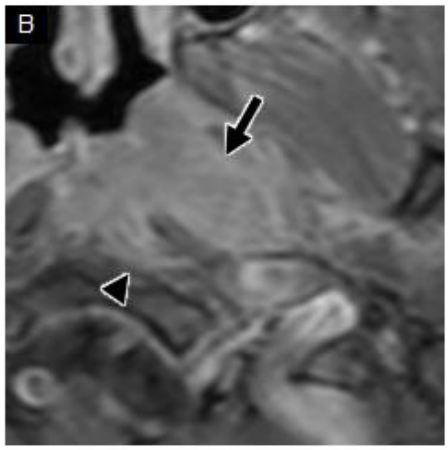
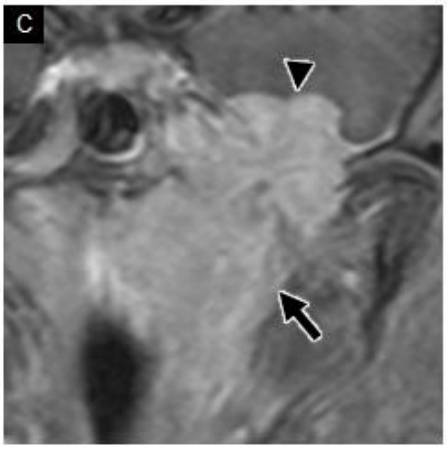


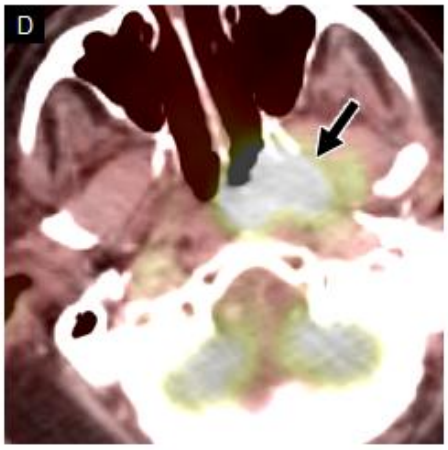
Figure 3. 31-year-old man with recurrent inverted papilloma status post multiple prior resections. Coronal bone NECT (A) shows lobular left nasal soft tissue

thickening (white arrow) with associated osseous remodeling and rarefaction (white arrowheads). Coronal T1WI C+ (B) shows a corresponding lobular enhancing mass (white arrow) extending into the postoperative ethmoid air cells with opacification of the left frontal sinus (black arrow) due to obstruction at the frontal recess. Axial T2WI FS MRI (C) shows the mass to be markedly hypointense (white arrow), concerning for a high cellularity tumor. Coronal 18F-FDG PET/CT (D) shows the mass to be mildly FDG avid (black arrow) relative to the surrounding sinonasal mucosa, but less FDG avid than the nearby brain parenchyma (black arrowhead). The FDG avidity of the mass was concerning for an occult squamous cell carcinoma harbored by the recurrent inverted papilloma; however, at resection no malignancy was found.









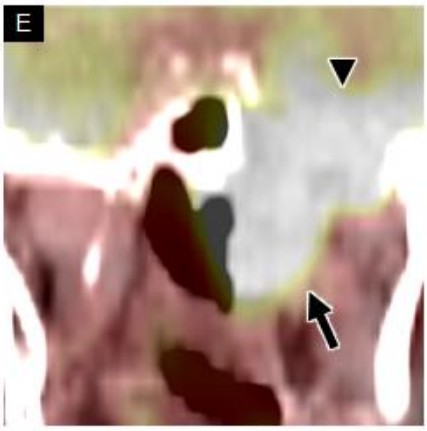
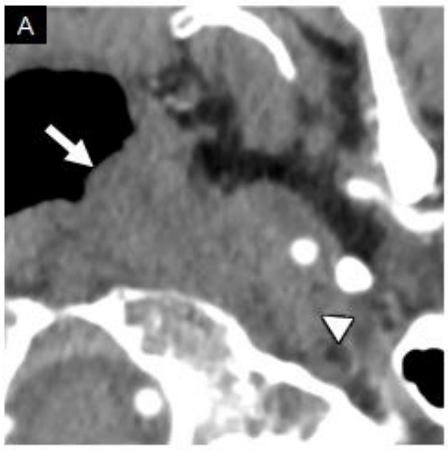
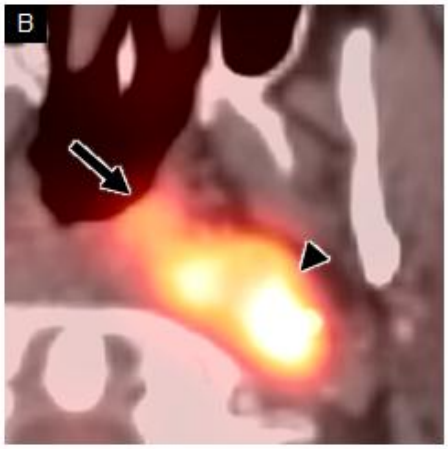


Figure 4. 72-year-old man with poorly differentiated nonkeratinizing squamous cell carcinoma of the nasopharynx (HPV-related). Axial temporal bone NECT (A) shows osseous destruction along the left skull base (white arrows). Axial T1WI C+ FS MRI (B) demonstrates a left nasopharyngeal mass (black arrow) with invasion of the left prevertebral soft tissues (black arrowhead) and extension along the skull base. Coronal T1WI C+ FS MRI (C) better delineates the skull base and intracranial extension (black arrowhead) of the left nasopharyngeal mass (black arrow). Axial 18F-FDG PET/CT (D) shows the left nasopharyngeal mass to be markedly FDG avid (black arrow). Coronal 18F-FDG PET/CT (E) shows the intracranial extension (black arrowhead) of the left nasopharyngeal mass (black arrow), but is markedly limited in differentiating FDG avid tumor from normal FDG avidity in the brain.





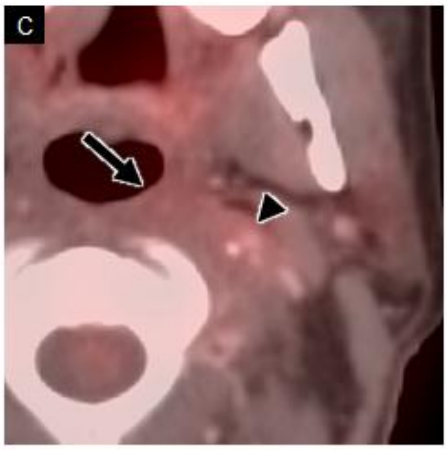
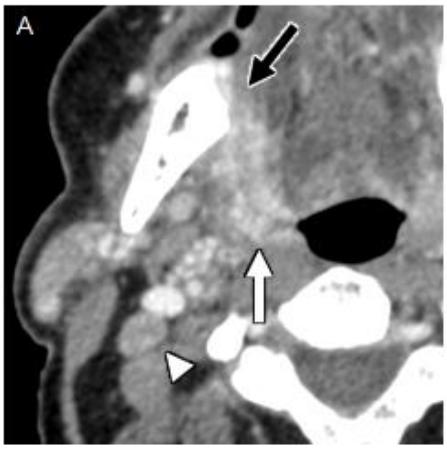
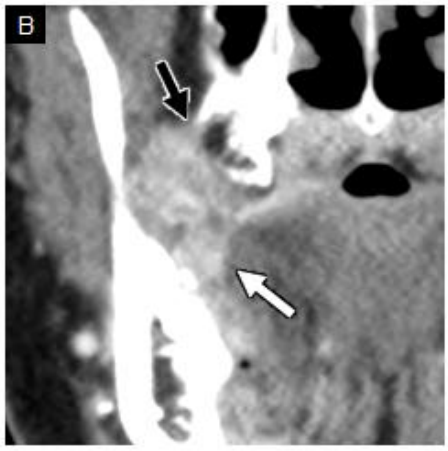
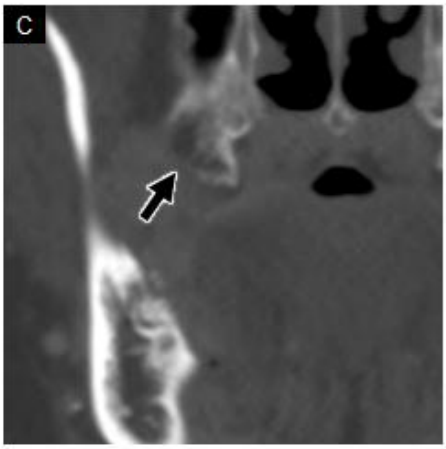
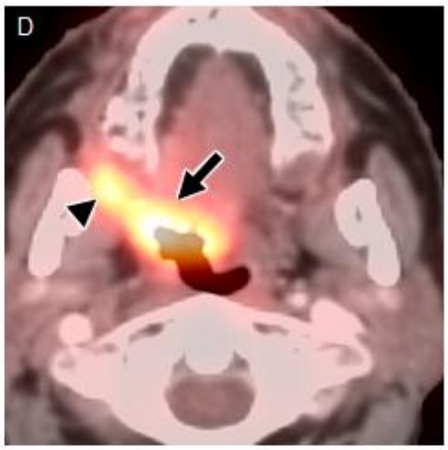


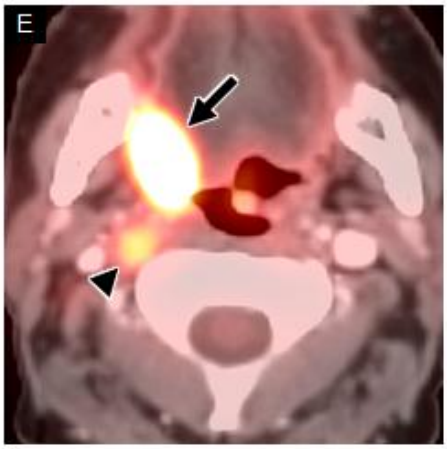
Figure 5. 65-year-old man with moderately to poorly differentiated nonkeratinizing squamous cell carcinoma of the left nasopharynx (HPV related). Axial CECT (A) shows a left nasopharyngeal mass (white arrow) with abnormal soft tissue thickening extending posterolaterally (white arrowhead). Pretreatment axial 18F-FDG PET/CT shows corresponding FDG avidity in the pharyngeal recess of the left nasopharynx (black arrow), as well as FDG avid tumor extending posteromedial toward the left carotid space (black arrowhead). 6-month post-treatment axial 18F-FDG PET/CT (C) shows no significant FDG uptake at the primary mucosal site (black arrow), as well as no significant FDG uptake corresponding to persistent mild left lateral retropharyngeal soft tissue (black arrowhead), consistent with treated disease.

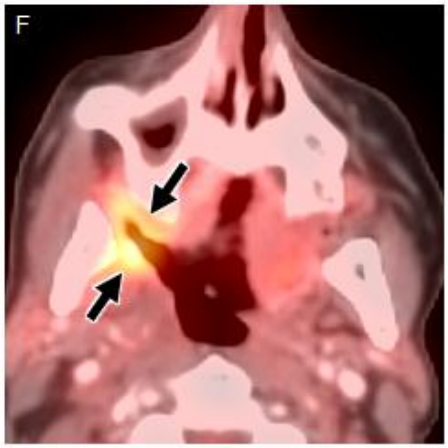












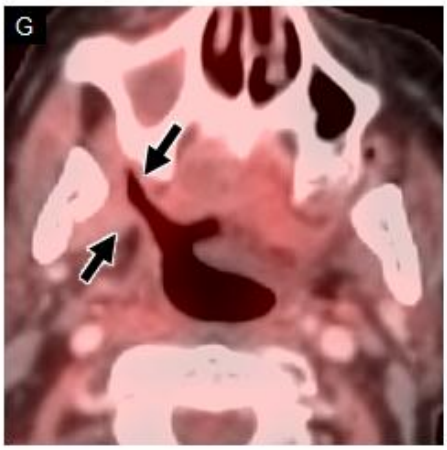
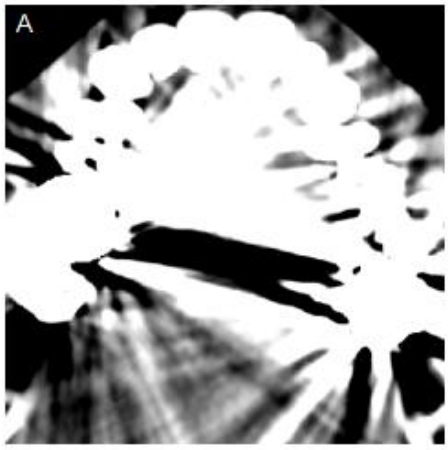
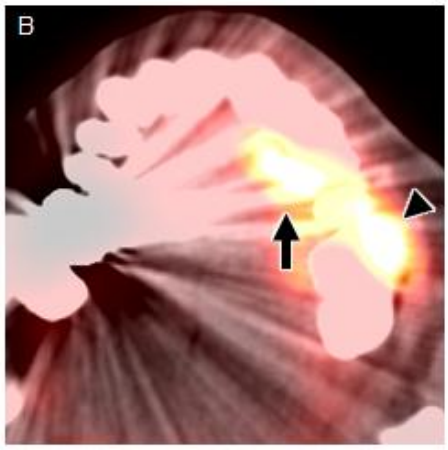


Figure 6. 58-year-old man with T4aN2cM0 poorly differentiated invasive squamous cell carcinoma of the right palatine tonsil. Axial CECT (A) shows an invasive right palatine tonsil mass (white arrow) with extension to the retromolar trigone (black arrow), as well as a morphologically suspicious, rounded right leel IIA lymph node (white arrowhead). Coronal CECT (B) shows the lateral extension of the mass to the right retromolar trigone (white arrow), as well as extension along the right maxillary alveolus (black arrow). Coronal bone kernel reconstruction (C) shows cortical erosion along the maxillary alveolus (black arrow). Axial F18-FDG PET/CT (D) shows the marked FDG avidity of the right tonsilar mass (black arrow), as well as the deep invasion of FDG avid tumor to the retromolar trigone (black arrowhead). Additional axial F18-FDG PET/CT (E) shows extension of FDG avid tumor along the right glossotonsilar sulcus (black arrow), as well as confirms previously suspected metastatic adenopathy at the

level IIA station (black arrowhead). 5-month post-treatment axial F18-FDG PET/CT (F) shows persistent moderately elevated FDG avidity in the region of previously treated mass (black arrows), which was biopsy confirmed as residual or recurrent disease. The patient continued chemoradiation, and 12-month post-treatment axial F18-FDG PET/CT (G) shows no residual hypermetabolic disease (black arrows).





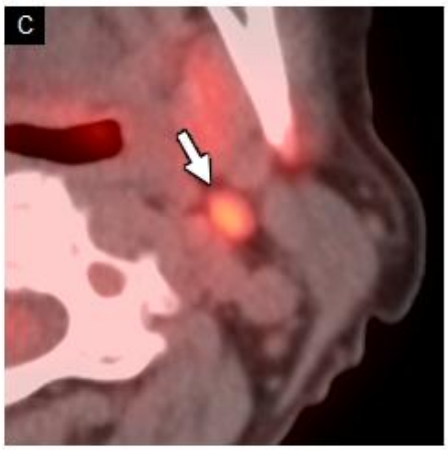
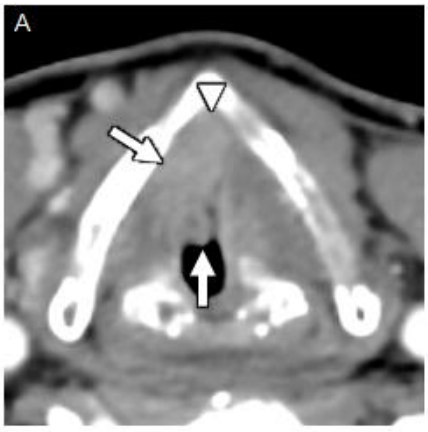


Figure 7. 80-year-old woman with poorly differentiated squamous cell carcinoma of the oral cavity. Axial CECT through the oral cavity (A) shows marked streak

artifact from the patient's numerous dental restorations, which obscures the oral cavity. Axial F18-FDG PET/CT shows a large oral cavity mass that extends along both the lingual (black arrow) and buccal (black arrowhead) surfaces. Additional axial F18-FDG PET/CT shows a nonenlarged, but FDG avid left level IIA lymph node (white arrow) representing nodal metastasis.



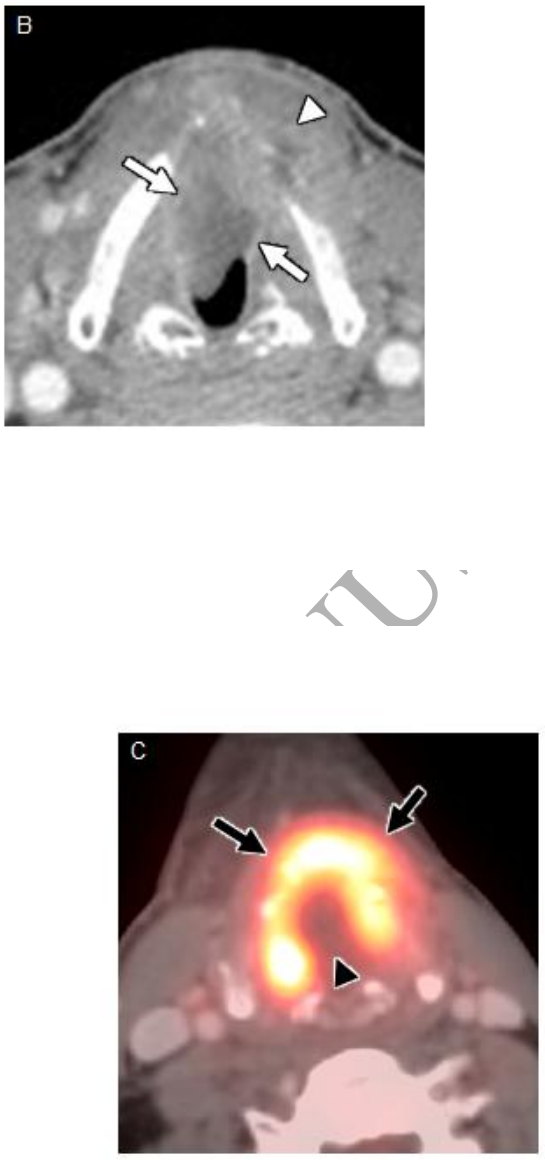
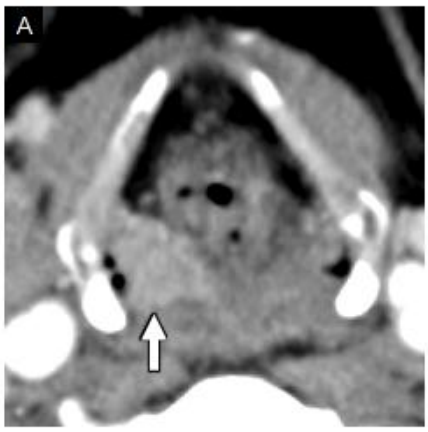
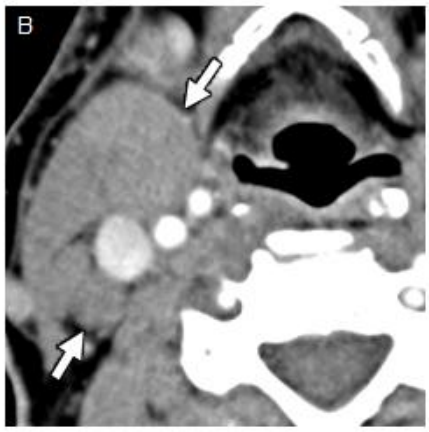


Figure 8. 50-year-old man with T2N0M0 poorly-differentiated squamous cell carcinoma of the supraglottic and glottic larynx. Axial CECT (A) shows an irregular-shaped mass centered in the right true vocal fold (white arrows), which extends to the anterior commissure (white arrowhead). The patient was lost to

follow-up and returned 6 months later, when a repeat axial CECT (B) shows marked interval enlargement of the laryngeal mass (white arrows), which now crosses midline and demonstrates extralaryngeal extension through the thyroid cartilage and into the overlying strap musculature (white arrowhead). A follow-up axial 18F-FDG PET/CT (C) performed 6 months later shows marked, diffuse FDG avidity throughout the glottic larynx (black arrows) corresponding to the enlarging mass. Lack of FDG uptake centrally (black arrowhead) is due to necrosis of the tumor centrally.





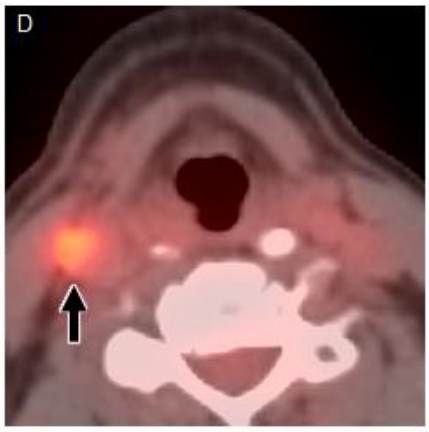
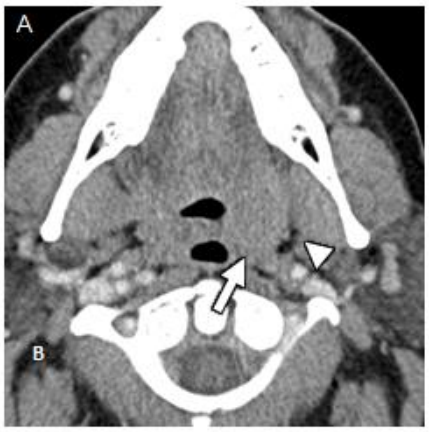
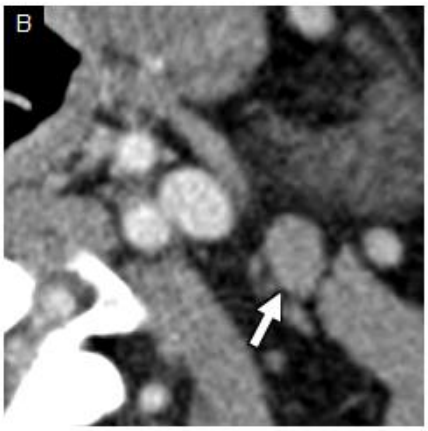
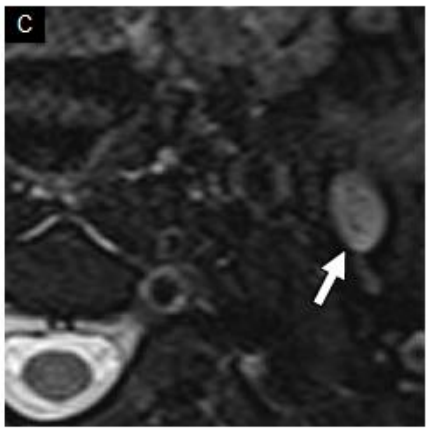


Figure 9. 65-year-old man with T2N2bM0 moderately differentiated, HPV negative squamous cell carcinoma of the right hypopharynx. Axial CECT (A) shows an avidly enhancing mass centered in the right pyriform sinus (white arrow). Additional axial CECT (B) shows enlarged right level III lymph nodes (white arrows), which are highly concerning for nodal metastases. Pretreatment axial F18-FDG PET/CT (C) shows marked FDG avidity corresponding to the hypopharyngeal mass (black arrow), as well as FDG avidity within a right neck nodal metastasis (black arrowhead). The patient underwent chemoradiation with resolution of the primary hypopharyngeal malignancy (not shown), but post-treatment axial F18-FDG PET/CT (D) showed persistent FDG avidity in right neck metastatic adenopathy (black arrow) due to residual disease.







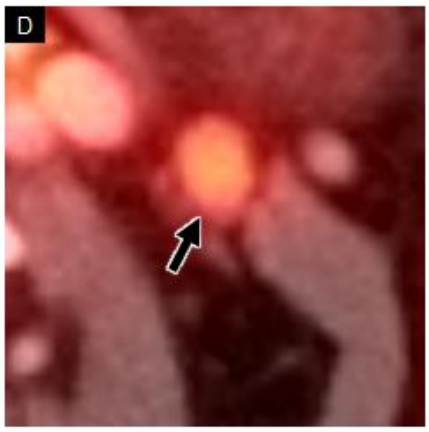
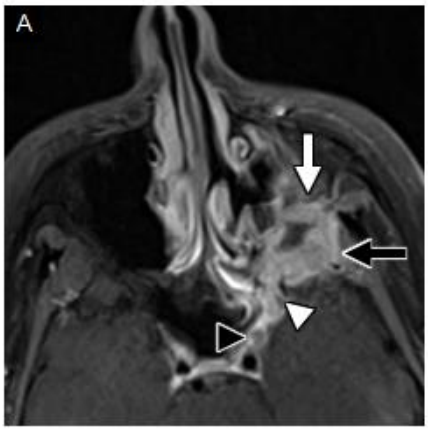
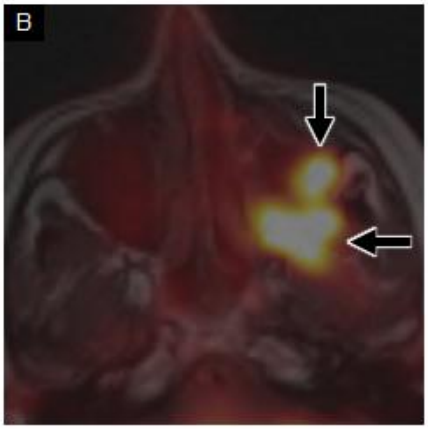


Figure 10. 38-year-old man with pT2pN2bM0 invasive squamous cell carcinoma of the left palatine tonsil, HPV 16/18 positive. Axial CECT (A) shows marked asymmetric enlargement of the left palatine tonsil (white arrow) with associated effacement of the left parapharyngeal fat (white arrowhead). Additional axial

CECT (B) identifies a non-enlarged left level IIB lymph node (white arrow), which is suspicious based upon its morphology with lack of fatty hilum and rounded contour. Axial T2WI FS (C) identifies the same morphologically suspicious lymph node (white arrow), which is mildly heterogeneous in signal intensity, but not conclusive for nodal metastasis on the conventional CT and MR imaging. Pretreatment axial F18-FDG PET/CT (D) shows increased FDG avidity in the same left level II lymph node (black arrow), increasing confidence in predicting metastatic adenopathy, which was confirmed at time of neck dissection.





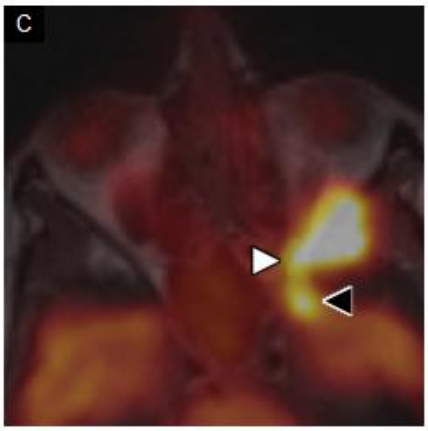
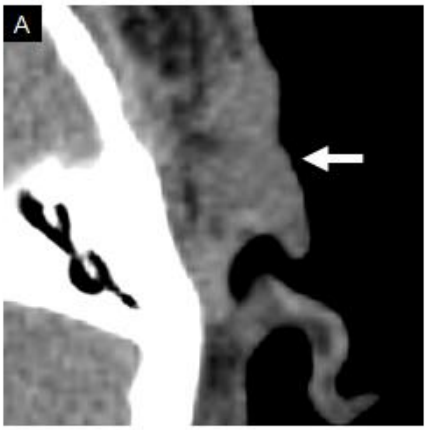
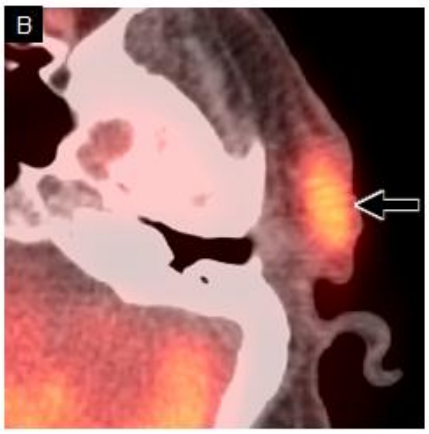
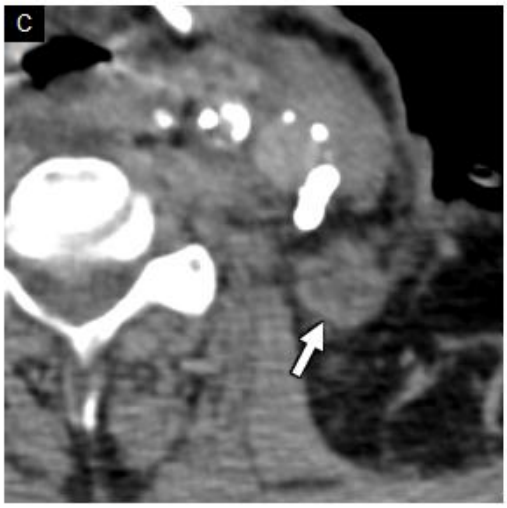
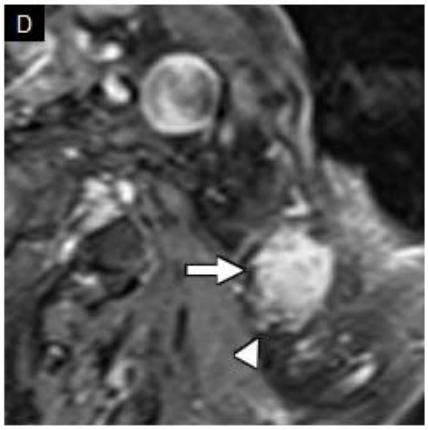


Figure 11. 61-year-old man with aggressive left maxillary sinus squamous cell carcinoma. Axial T1WI C+ FS MRI (A) shows an enhancing mass centered within the left maxillary sinus (white arrow) with tumor extension into the left infrazygomatic masticator space (black arrow), retromaxillary fat, and pterygopalatine fossa. Note addititional perineural tumor spread along CNV2 in the foramen rotundum (white arrowhead) with extension to the anterior cavernous sinus (black arrowhead). Axial 18F-FDG PET/MR with fused T1WI (B) confirms hypermetabolic tumor in these locations (black arrows), as well as (C) delineates perineural tumor spread along CNV2 in the foramen rotundum (black arrowhead) and invading the inferior orbital fissure (white arrowhead).









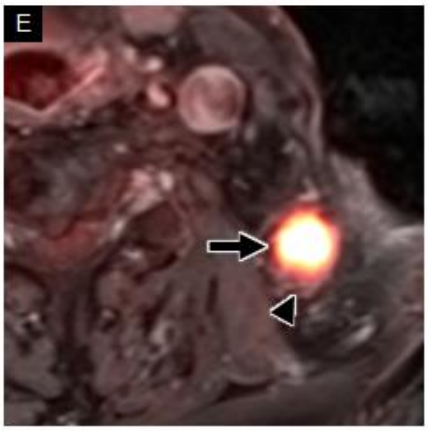


Figure 12. 75-year-old male with invasive squamous cell carcinoma of the left temporal scalp. Axial NECT (A) shows an invasive left preauricular skin cancer (white arrow) with deep invasion into the subcutaneous tissues. Axial 18F-FDG PET/CT (B) demonstrates marked FDG avidity within the primary tumor (black arrow), which was subsquently resected. A follow up axial CECT performed 3 years later (C) shows a highly concerning, enlarged left level V lymph node (white arrow) with rounded morphology and loss of fatty hilum. Axial T1WI C+ FS (D) shows this lymph node to have concerning heterogeneous hyperenhancement (white arrow), including shaggy enhancement at its margin (white arrowhead), concerning for extranodal extension (ENE) of tumor. Axial 18F-FDG PET/MRI with fused T1WI C+ FS (E) shows associated hypermetabolism within the level V node (black arrow), as well as mildly increased FDG uptake in the adjacent enhancing soft tissue (black arrowhead), which remains concerning for ENE.