

# The current role of imaging in head and neck cancer: a clinician's perspective

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## Summary

Imaging head and neck cancer is crucial for treatment decisions and follow-up of patients. The choice of the appropriate imaging modality for staging and re-staging head and neck cancer can be troublesome. This review highlights the important questions of imaging from a clinician's perspective. The recommendations focus on mucosal squamous cell carcinoma of the head and neck since this is the most common one.

**Key words:** *Imaging; head and neck; squamous cell carcinoma; ultrasound; 18F-FDG-PET/CT*

## Introduction

With an incidence of 500,000 new cases a year, malignant tumours of the head and neck rank fifth of all carcinomas [1]. Malignant epithelial tumours of the head and neck are histologically divided in verrucous carcinomas, spindle cell carcinomas, adenocarcinoma, adenosquamous carcinoma, lymphoepithelial carcinoma, giant cell carcinoma, malignant salivary gland-type tumours and squamous cell carcinomas. Head and neck squamous cell cancer (HNSCC), the most common one with over 90%. Over 300,000 deaths worldwide and around 450 deaths in Switzerland occur every year due to this type of cancer [1, 2]. There is a geographic variety due to different risk factors [3]. 80% of HNSCC in the eastern world are located in the oral cavity and (nasal-) pharynx, whereas the carcinoma of the larynx takes over a third of all HNSCC in the western world [4]. The mean age of primary HNSCC diagnosis is about 60 years, yet the incidence of younger patients is increasing [5]. In most countries men more often contract HNSCC than women [3]. Besides the risk factors alcohol and tobacco, infection with human papilloma virus (HPV) is an increasing independent risk factor for developing oropharyngeal squamous cell carcinomas (OPSCC) [6, 7]. The role of HPV in the pathogenesis of HNSCC was first described in 1983 [8]. Many studies suggest that patients with an HPV affected OPSCC have a better prognosis and argue that a customised therapeutic approach is warranted for those patients. Traditional therapy regimens of OPSCC, 9–11 high doses of radiation or chemotherapy, may be

an overtreatment for HPV-positive OPSCC, which is part of several clinical trials [12]. In general, the survival of HNSCC patients is mostly dependent on the stage of disease and personal medical health. Over 60% of the patients are at an advanced stage (Stage III and IV) at the time of diagnosis [13]. Therefore, adequate staging strategies including different imaging modalities are crucial to determine the stage of the disease and the directly related treatment strategy.

## Pre-operative staging

Assessing the primary tumour precisely is crucial for treatment planning and interdisciplinary therapy strategies. The surgeon's questions for assessing the primary are threefold: Firstly, the exact delineation and extension of the tumour, secondly, the potential infiltration of adjacent structures (e.g., vessels, cranial nerves), and thirdly, the differentiation between tumour infiltration and inflammatory reaction of surrounding tissue. Furthermore, there might be the scenario when the primary tumour is missing, so called

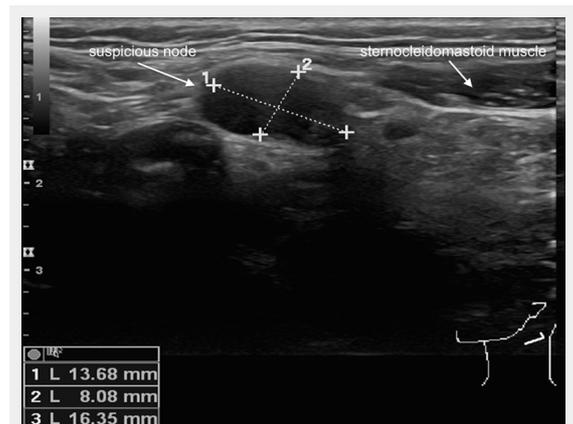


Figure 1

Sonographic appearance of a suspicious lymph node on palpation in level II left from a patient with a small squamous cell carcinoma of the right lateral tongue. The absence of an echogenic hilus, the size of more than 1.5cm and the shape of the lymph node renders it sonographically suspicious. The cytology result after ultrasound-guided fine needle aspiration confirms the presence of a contralateral positive node.

'cancer of unknown primary' (CUP). Many reports could show for staging purposes of the primary local extension and its related questions are best seen on contrast-enhanced (Ce) computed tomography (CT) or magnetic resonance imaging (MRI) [14]. Soft tissue definition, perineural spread, skull base invasion, intracranial extension, vascularisation and potential bone involvement is best evaluated with MRI [15, 16]. CeCT scans provide a great resolution, are fast and show exact details in bony structures. In clinical examination detection of deeper local invasion or infiltration in structures nearby of cancers is limited. Furthermore, ceCT is particularly useful because criteria for T4 classification like bone or cartilage invasion can be shown [17]. The addition of contrast-agent is crucial since cystic or necrotic lesions may be missed with a native CT scan [18]. In case of CUP, recent studies were able to show the benefit of using metabolic imaging. In up to 30% of cases with cervical lymph node involvement without a corresponding primary when clinical exam and conventional imaging (CT, MRI) are not able to reveal the primary tumour, [18F] fluoro-2-deoxy-D-glucose (18F-FDG) positron emission tomography (PET) in combination with CT (PET/CT) is able to detect as such [19, 20]. Rudmik et al. 21 showed a change in treatment due to the detection of the primary by the use of metabolic imaging in 30%. This is significantly related to the patient's treatment plan and costs.

The classic approach to detect a CUP in the otolaryngologists eyes is to perform a panendoscopy (including direct pharyngoscopy, laryngoscopy, oesophagoscopy, and tracheo-bronchoscopy), taking blind biopsies from the base of tongue (BOT) and nasopharynx, performing uni- or bilateral tonsillectomy and obtain any kind of head and neck imaging. Having a 18F-FDG-PET/CT scan available in the operating room indicating the surgeon where to search and biopsy for the potential primary reduces the rate of missing primaries, the morbidity caused by blind biopsies, and therefore the patient's burden significantly. Consequently, the gold standard in case of CUP shall be to obtain a 18F-FDG-PET/CT scan prior to panendoscopy with the warranted biopsies.

Regional lymphatic involvement for patients suffering from HNSCC is the strongest prognostic factor in these patients [22]. Patients with no nodal involvement count for a 5-year survival of 63% to 86%, whereas 5-year survival rates of 20–36% for patients with lymph node metastases are noted [23]. Clinical examination and appropriate imaging leads to optimal clinical staging and classification of the neck, which has important impact on the treatment decision regarding surgical and non-surgical treatment options. The staging options for patients with a clinical negative neck are manifold and there is a lack of prospective comparative studies in homogeneous patient cohorts with uniform inclusion criteria for the evaluation of the most accurate imaging modality- Ultrasound-guided fine needle aspiration cytology (USgFNAC) seems to correlate best with the exact histologic staging (fig. 1) [24]. There is a correlated sensitivity regarding this technique with the investigator's skills [25]. However, there seems to be an increasing number of head and neck Surgeons performing neck ultrasounds by themselves. Most centres throughout

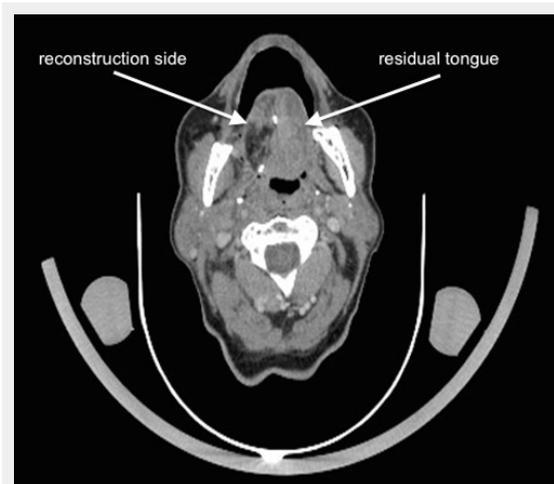
the world still perform a CT scan if ultrasound is not available in an office-based set up. Since the primary tumour cannot be assessed using ultrasound there is no doubt performing a CT scan for staging reasons is arguable. However, as stated above, maybe the primary will better be assessed by an MRI. Contrast-enhanced CT and MRI are the methods of choice to evaluate the primary tumour, but their accuracy for nodal metastases is discussed in recent reports [26]. Therefore the authors advocate performing an ultrasound of the neck, and, if necessary, an USgFNAC, for staging the clinical N0 neck. In surgical cases patients with a clinical N0-neck should be offered minimally invasive sentinel node biopsy (SNB) [27] or risk-level-based elective neck dissections (ENDs) [28] for most accurate staging purposes. There is a different algorithm if patients present with clinically positive neck involvement. More than a single node is involved (N2b or N2c) or an involved lymph node of more than 3cm in maximum diameter (N2a or N3) is related with a higher risk of distant metastases, and therefore, 18F-FDG-PET/CT is indicated to exclude such [29]. Nevertheless, because of its low costs and its additional value for the assessment of the neck, a neck ultrasound will be added at our institution. For surgical candidates, final staging will be completed after histological assessment of the tissue specimen obtained from the neck dissection specimen [30]. On the other hand, in patients who receive a primary (chemo) radiation, the staging of the neck is 'solely' based on imaging. In these cases, the authors advocate performing metabolic imaging for two reasons: First, the metabolic information retrieved from a 18F-FDG-PET/CT can be further used for dose-painting in the planning phase, and second, treatment response after therapy can be assessed by using the metabolic part of the multimodality imaging [31, 32].

In general, advanced tumours (T3/T4 and/or N2/3), laryngopharyngeal tumours, and low level involved lymph node metastases (level III/IV) harbour a high risk of distant disease, and for all patients with such disease, a 18F-FDG-PET/CT scan should be added to exclude distant metastasis [29]. Further, due to alcohol and nicotine abuse which is often encountered in patients with HNSCC they have an increased risk of developing synchronous and metachronous SCC in other regions of the upper aerodigestive tract [33]. Therefore, again, metabolic imaging should be added to exclude second primaries in advanced staged tumours. For small tumours in patients without risk factors panendoscopy performed by the head and neck surgeon is sufficient. In cases of advanced tumours and a negative 18F-FDG-PET/CT regarding second primaries, panendoscopy can be reduced to endoscopic assessment of the primary tumour only. In these cases it is important to perform metabolic imaging prior to planned panendoscopy [29].

## Post-treatment imaging and re-staging

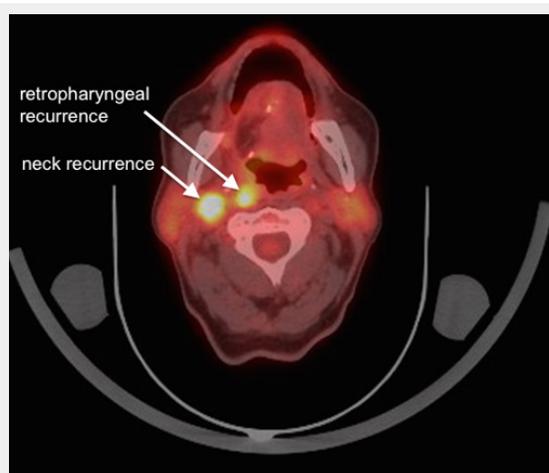
HNSCC is treated in many different ways. Small primaries with a clinical N0-neck or small volume regional disease is either treated surgically or with primary irradiation depending on tumour location and/or relevant patient's comorbidities. On the other hand advanced tumours are mostly

treated in a combined approach meaning surgery plus (chemo-) irradiation or vice versa. In either treatment setting imaging plays an important role in the clinician's view. Post-treatment imaging is mostly used to monitor treatment response and to detect persistent or recurrent disease. Patients who received potential curative treatment for HNSCC are at risk for recurrence between <10% and up to 48% [34, 35]. Most recurrent disease, second primary tumours or metastases occur within 2–3 years after initial treatment [36–38]. Early tumour recurrence may be difficult to confine from tissue changes induced by therapy. For initially early staged disease without any neck involvement (e.g., laryngeal SCC cT1 cN0) post-treatment ima-



**Figure 2**

Follow-up contrast enhanced computed tomography part from a 18F-FDG-PET/CT scan 6 months following right partial glossectomy, elective neck dissection and reconstruction of the tongue with a radial forearm free flap for a pT2 pN1 squamous cell carcinoma. The primary site cannot be evaluated exactly regarding local recurrence. There are no evident suspicious lymph nodes to be detected.



**Figure 3**

The same follow-up 18F-FDG-PET/CT scan showing the fused 18F-FDG-PET part with the CT part. There is no evidence for local recurrence at the reconstruction site however there are two highly suspicious lymph nodes in level IIb ipsilateral and retropharyngeal.

ging may not be warranted routinely. For small disease with lymphatic involvement conventional imaging (CT or MRI) of the primary will be the first choice for post-treatment imaging. As stated previously, the neck is best addressed by USgFNAC as a baseline and follow-up imaging [39]. Various studies not only show a superior efficacy of US and USgFNAC in the follow-up of the treated neck, but also that USgFNAC is superior to CT in detecting recurrent disease [39–41]. It is generally recommended that the post-treatment baseline CT/MRI should be performed three to six months after treatment. In general, the same imaging modality as the pre-treatment study should be used as subsequent imaging [42, 43]. This first baseline imaging scan demonstrates treatment-caused changes in the tissue, which render accurate interpretation between treatment changes and residual disease difficult [44–46]. A part of the routine follow-up of HNSCC is imaging the chest to detect lung metastasis and second primaries in the lung [47]. CT is shown to be superior as a screening tool to detect lung malignancies in comparison to a normal chest radiograph. Therefore chest CT seems to be necessary for the follow-up of high risk patients [48–50]. In the era of metabolic imaging, again, in high risk patients the chest will be examined as part of a 'one stop shop strategy' in the context of 18F-FDG-PET/CT.

After (chemo-) radiation tumour recurrence appears as a tissue mass at the primary site on CT or MRI. However, distinguishing between persistent viable tumour tissue and posttherapeutic changes can be difficult [51]. MRI is recommended for patients with base of tongue, sinonasal, skull base and nasopharyngeal tumours and with suspicion of perineural or intracranial spreading [52]. Diffusion-weighted MRI (DW-MRI) was shown to be even superior to anatomical imaging [53]. 18F-FDG-PET/CT has also found widespread acceptance for restaging after radiotherapy and chemo-radiotherapy [54, 55]. It was seen that the effectiveness of 18F-FDG-PET/CT in detecting recurrence or relapse leads to a specificity of 94%, the positive predictive value was 75%, the negative predictive value 95% and the sensitivity was greater for scans performed after 10 weeks of treatment [56–58]. The accuracy of 18F-FDG-PET/CT for distant metastasis in patients with laryngeal cancer is almost 100% [59]. 18F-FDG-PET alone shows a high ratio of false positive results in patients with suspected recurrent disease. The combination of 18F-FDG-PET with a ceCT part reduces these false positive rates by over 50% compared to CT alone [60]. The high negative predictive value suggests that salvage surgery can be avoided in many cases [60–62].

In the case of a combined treatment for advanced lesions a repeated 18F-FDG-PET/CT scan is indicated to evaluate treatment response and further follow-up. Since metabolic imaging was indicated at the time of diagnosis to exclude distant disease or second primaries, it is advantageous to repeat the same scan post treatment for distinctive comparison. There are no guidelines for optimal timing of the post-treatment 18F-FDG-PET/CT. Overall, recent studies show a tendency towards a greater sensitivity for 18F-FDG PET/CT performed 10 weeks or more after treatment. Therefore, it shouldn't be performed earlier than two to three months after treatment [56, 63–66]. There is still a debate about the

benefit of ongoing surveillance scans. In a previous publication the authors were able to show significance in outcome between patients with or without distant disease. However, the time of diagnosis did not play any significant role [29]. Head and neck cancer patients with a negative first post-treatment scan (e.g., after three months) appear to derive limited benefit from subsequent 18F-FDG PET/CT surveillance [67].

Since there are some difficulties in the interpretation of these scans due to scarring and inflammation after surgery as well as irradiation of the tissue repeated scans may be indicated. Furthermore, complex reconstructions may result in diffuse FDG-uptake rendering a definitive diagnosis difficult and repeated biopsies of the suspicious areas may be necessary.

After all there is no consensus of the perfect time for baseline and follow-up imaging. At our institution first imaging will be done 10 weeks after treatment. After that follow-up imaging is based on the previous findings. Since locoregional recurrence is often seen during the first two years after initial treatment the authors feel there is a legitimate reason for another subsequent scan, e.g., after 12, and 24 months. 18F-FDG-PET/CT is shown to be more accurate than conventional follow-up imaging alone regarding the detection rate of recurrences (fig. 2, and 3) [68]. Any additional imaging modalities should be performed on clinical signs. Suspicious lymph nodes can best be evaluated with USgFNAC.

## Conclusions

The assessment of the primary tumour with CT or MRI will always be completed with ultrasound-guided FNAC for the assessment of the neck, because it seems to correlate best with the exact histologic staging. In surgical cases a patient with a clinical negative neck should be offered minimally invasive SNB or risk-level-based ENDS. In patients with advanced tumour stages 18F-FDG-PET/CT will be performed as a one stop shop strategy for the exclusion of second primaries and distant metastases. In selected cases (e.g., base of tongue cancer), the locoregional assessment warrants the addition of a MRI. In case of cancer of unknown primary 18F-FDG-PET/CT is the most accurate choice of imaging prior to panendoscopy with biopsies.

The timely detection of residual or recurrent head and neck cancer after therapy is important to allow a prompt salvage treatment. Besides clinical examination, post-treatment imaging is crucial for follow-up. A baseline post-treatment imaging study should be performed 10 weeks after therapy. As shown in studies above, 18F-FDG-PET/CT shows an advantage in detection of locoregional persistence, recurrence and distant disease. The positive predictive value of the 18F-FDG-PET/CT is somewhat suboptimal at the primary site and the neck. However, its negative predictive value remains extraordinary high, so that a negative finding in post-treatment follow-up imaging by 18F-FDG-PET/CT is highly suggestive of the absence of recurrence or distant disease. In case of suspicious lymph nodes at clinical/radiologic examination USgFNAC should be performed in any case.

**Funding / potential competing interests:** No financial support and no other potential conflict of interest relevant to this article were reported.

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Figures (large format)

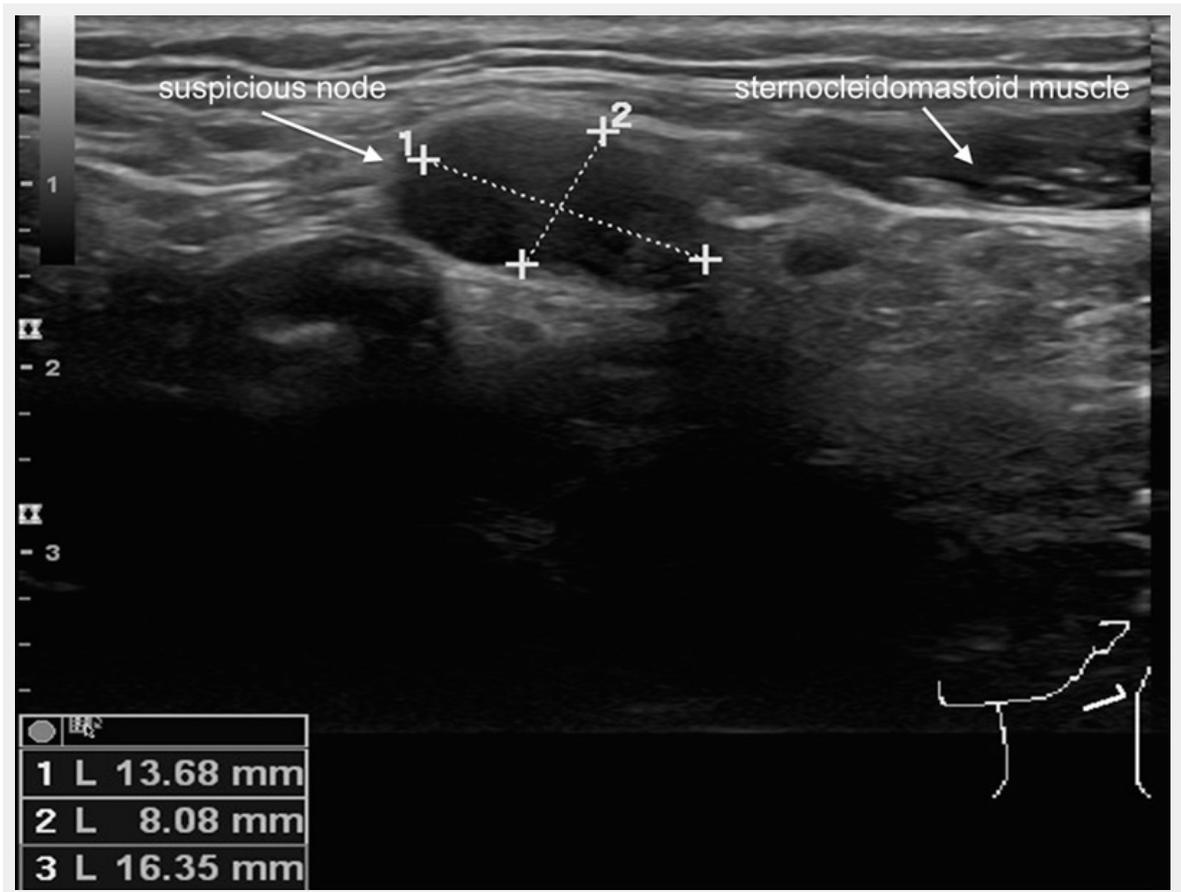
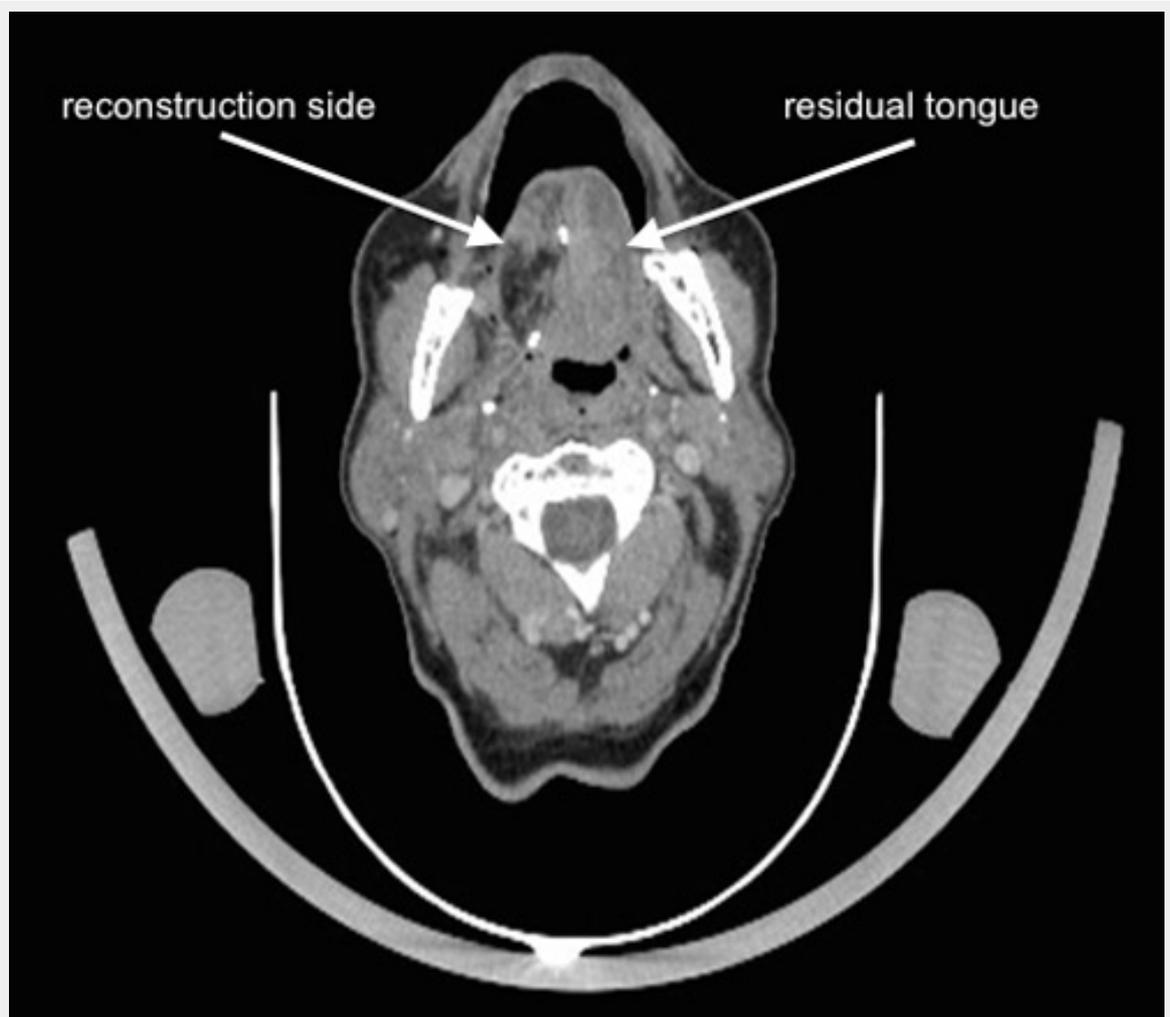


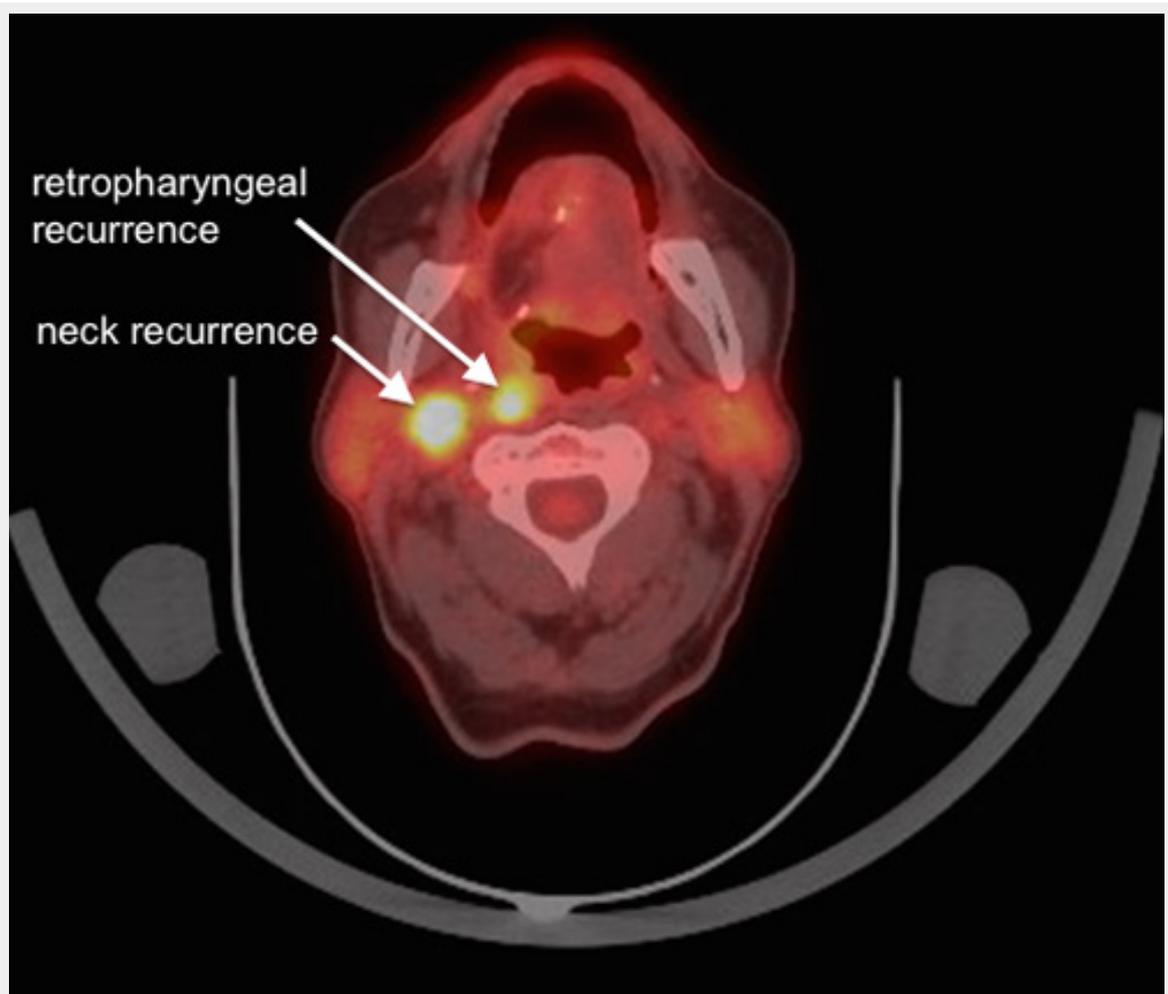
Figure 1

Sonographic appearance of a suspicious lymph node on palpation in level II left from a patient with a small squamous cell carcinoma of the right lateral tongue. The absence of an echogenic hilus, the size of more than 1.5cm and the shape of the lymph node renders it sonographically suspicious. The cytology result after ultrasound-guided fine needle aspiration confirms the presence of a contralateral positive node.



**Figure 2**

Follow-up contrast enhanced computed tomography part from a 18F-FDG-PET/CT scan 6 months following right partial glossectomy, elective neck dissection and reconstruction of the tongue with a radial forearm free flap for a pT2 pN1 squamous cell carcinoma. The primary site cannot be evaluated exactly regarding local recurrence. There are no evident suspicious lymph nodes to be detected.



**Figure 3**

The same follow-up 18F-FDG-PET/CT scan showing the fused 18F-FDG-PET part with the CT part. There is no evidence for local recurrence at the reconstruction site however there are two highly suspicious lymph nodes in level IIb ipsilateral and retropharyngeal.