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Original article

Comparison of positron emission tomography/computed tomography imaging and ultrasound in surveillance of head and neck cancer – The 3-year experience of the ENT Department in Poznan

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ABSTRACT

Background: Posttreatment surveillance for the local and regional recurrence of the head and neck squamous cell carcinoma often requires a multimodality techniques that include PET combined with CT, MRI, US.
Aim: The purpose of this study is to compare the diagnostic performance of two imaging techniques (PET/CT and US), and their combined use for the detection of a subclinical regional recurrence in patients after HNSCC treatment.
Materials and methods: 83 patients after completion of the HNSCC treatment underwent both US and PET/CT on the mean follow-up of 14 months after initial treatment.
Results: The sensitivity and specificity of PET/CT were 86% and 82%, respectively; US values reached 81% and 87%, respectively. PPV was 79% for PET/CT, and 83% for US. NPV was 89% for PET/CT, and 85% for US. The overall accuracy for PET/CT and US was 84% for both methods.
Conclusion: US could be regarded as complementary to PET/CT as the procedures with highest sensitivity, specificity and NPV for detecting subclinical regional recurrences after HNSCC treatment.
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1. Background

Head and neck squamous cell carcinoma is the sixth most common malignancy in Europe[1] and refers to a group of malignancies involving the upper aerodigestive tract, including the oral cavity, oropharynx, nasopharynx, hypopharynx, and larynx. Treatment often requires a multimodality approach that includes combinations of surgery, radiation, and chemotherapy. Such treatment frequently causes significant distortions

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of normal tissues, such as edema or fibrosis, which may obscure an early detection of recurrent disease and postpone a subsequent salvage treatment.Positron emission tomography (PET) with fluorine 18-fluorodeoxyglucose (FDG) combined with computed tomography (CT) enable highly precise localization of the metabolic abnormalities, which cannot be achieved with conventional morphologic imaging such as computed tomography (CT) and magnetic resonance (MRI).[2–4]

Ultrasonography (US) has been widely used for the assessment of the cervical lymph node status both in staging and posttreatment evaluation.[5]

To the best of our knowledge, many studies have investigated the accuracy of above mentioned modalities for staging of the tumor, but the actual usefulness of combined use of PET/CT and US has not yet been determined in the posttreatment surveillance for the regional recurrence of the head and neck squamous cell carcinoma (HNSCC).

2. Aim

Based on the fact that the incidence of distant metastases, survival, and tumor control are dependent on the status of cervical lymph nodes,[6] the purpose of this retrospective study was to compare the diagnostic performance of two imaging techniques (PET/CT and US), and their combined use for the detection of a subclinical regional recurrence in patients after HNSCC treatment.

3. Material and methods

3.1. *Patients*

Between December 2007 and April 2010, 83 patients, who had completed their HNSCC treatment, underwent US in the ENT-Department in Poznan and PET/CT in the PET/CT Center in Poznan and Warsaw. All patients completed these two examinations (PET/CT and US) at the mean follow-up of 14 months (minimum 5, maximum 22 months) after initial treatment. Additionally, clinical otolaryngological examination did not reveal any suggestion of recurrence in any of the patients under study.

The diagnosis of SCC was proved pathologically in all patients. Table 1 shows primary tumor sites, i.e. the larynx ($n = 20$), pharynx ($n = 9$), tonsil ($n = 6$), tongue ($n = 10$), oral cavity ($n = 17$), skin ($n = 3$), maxillary region ($n = 10$), and others ($n = 8$). All patients underwent a complete resection of the primary tumor or a debulking procedure, depending on the initial size of the tumor. Size of the tumor (T) is also presented in Table 1 (7 patients had T1, 26 – T2, 14 – T3, 36 – T4). All patients were also treated with the neck dissections, which were determined based on the clinical and imaging findings estimating the size and number of the lymph nodes (N).

Table 1 – Primary tumor site, stage and nodal status in patients treated in ENT Department in Poznan due to HNSCC.

Age (years)	
Mean range	57
Sex	
Male	64
Female	19
Total	83
Tumor site	
Oral cavity	36
Oropharynx	3
Hypopharynx	6
Larynx	20
Salivary gland	7
Nasal cavity and paranasal sinuses	11
Tumor stage	
T1	7
T2	26
T3	14
T4	36
Nodal status	
N0	39
N1	12
N2	21
N3	11

3.2. *Imaging techniques*

3.2.1. PET/CT

All the data were acquired with a combined PET/CT system (Discovery ST, GE Health Systems, Milwaukee, WI), permitting the acquisition of co-registered CT and PET images in one session.

Patients fasted for at least 4 h preceding the scanning, which started 60 min after the injection of 18F-FDG. All patients were tested for a normal glucose level [range 80–120 mg/dl (4.4–6.7 mmol/l)] before scanning. Patients with elevated glucose levels were rescheduled and scanned with normal glucose levels. Oral CT contrast agent (Gastrografin, Schering, Germany) was given before the injection of 18F-FDG. Patients were examined in the supine position. No intravenous contrast agent was given. Initially, the CT scan was acquired starting from the level of the head using the following parameters: 40 mAs, 140 kV, 0.5 s/tube rotation, slice thickness 4.25 mm. Immediately following the CT acquisition, a PET emission scan was acquired with an acquisition time of 2.5 min per cradle position with a one-slice overlap in 3D mode. The eight cradle positions starting from the head to the knees resulted in an acquisition time of approximately 20 min. The CT data were used for attenuation correction of the PET datasets and the images were reconstructed using a standard iterative algorithm (OSEM). The acquired images were viewed with software providing multiplanar reformatted images of PET alone, CT alone and fused PET/CT using the Advantage Workstation (GE Health Systems, Milwaukee, WI).

3.3. *US*

US examinations were performed using an Aloka SSD1700 ultrasonographer (Japan, Tokyo Diagnostic Ultrasound System) with a 7.5-MHz liner transducer probe. Color Doppler US was performed with low flow settings for optimal detection of signals from lymph node vessels.

Table 2 – PET/CT and US results for detecting regional recurrence of HNSCC.

Primary tumor site	PET/CT for regional recurrence				USG for regional recurrence			
	TP	FP	TN	FN	TP	FP	TN	FN
Oral cavity	15	3	15	3	15	1	16	4
Oropharynx	–	1	2	–	–	1	2	–
Hypopharynx	1	2	3		3	1	1	1
Larynx	7	–	11	2	4	1	14	1
Salivary glands	4	–	3	–	4	2	1	–
Nasal cavity and paranasal sinuses	4	2	5	–	3	–	7	1
Total	31	8	39	5	29	6	41	7

TP: true positive; FP: false positive; TN: true negative; FN: false negative.

3.4. *Image interpretation*

The PET/CT images were reviewed and analyzed by two experienced physicians: nuclear medicine physician and radiologist. For all of the patients, the attenuation-corrected PET images were reviewed as maximum intensity projections and in transaxial, coronal, and sagittal planes. The PET images and the corresponding CT images of the PET/CT study were analyzed for the presence of focal lesions with elevated ^{18}F-FDG uptake. Lesions were interpreted as metabolically positive if the ^{18}F-FDG standardized uptake value was greater than 3.0. If a focal FDG-active lesion was detected, the exact anatomical localization was determined on the fused PET/CT images. The interpretation of active lesions was based on the location and morphology. Areas of physiological activity (e.g. muscles, brown adipose tissue, palatine tonsils, salivary glands) were excluded unless uptake was asymmetrical (right–left difference of SUV $\geq$ 1.0).Cervical lymph nodes visualized by US were considered to be metastatic, thus warranting suspicion of regional recurrence, if they showed the following criteria: a short axis diameter >7 mm, the long-to-short axis ratio < 2, absence of an echogenic hilum, and the absence of normal hilar blood flow and/or the presence of abnormal peripheral blood flow on color Doppler.[7–9]

4. Results

The study group consisted of 83 patients, 19 women and 64 men, with a mean age of 57. Patient pretreatment pathologic status is summarized in Table 1.

According to PET/CT, 36 patients had regional extension of malignant process. The results for the neck were true negative in 39 patients, true positive in 31, false positive in 8, and false negative in 5. US findings were true negative in 41 patients, true positive in 29, false positive in 6, and false negative in 7 (Table 2). Both PET/CT and US results were confirmed whether by open, explorative biopsy or fine needle aspiration. For 10 patients, salvage surgery was performed, 26 patients underwent chemotherapy, radiotherapy or palliative treatment.

As presented in Table 3, the sensitivity and specificity of imaging modalities in this study for the early diagnosis of HNSCC recurrence were 86% and 82%, respectively for PET/CT. For US, the values reached 81% and 87%, respectively. The positive predictive value (PPV) was 79% for PET/CT, and 83% for US. The negative predictive value (NPV) was 89% for PET/CT, and 85% for US. The overall accuracy for PET/CT and US was 84% for both methods.

Table 3 – Sensitivity, specificity, PPV, NPV, and accuracy of both PET/CT and US for regional HNSCC recurrence.

	PET/CT	USG
Sensitivity	86%	81%
Specificity	82%	87%
PPV	79%	83%
NPV	89%	85%
Accuracy	84%	84%

PPV: positive predictive value; NPV: negative predictive value.

5. Discussion

The highest incidence of HNSCC recurrence occur within 2 years after initial treatment.[10] A delay in the detection of recurrent HNSCC has been shown to have negative clinical outcome after treatment. Patients with recurrent, early-stage HNSCC who undergo salvage surgery have a 70% rate of 2-year relapse-free survival, whereas those with recurrent, advanced-stage HNSCC undergoing surgical salvage have just a 22% rate of 2-year relapse-free survival.[11] Early diagnosis and accurate identification of recurrent HNSCC are thus essential for successful treatment. Clinical examination and imaging are recommended at 1–3-month intervals (1–2-month intervals for tumors with aggressive histology) for the first year, at 2–4-months intervals during the second year, every 4–6 months during the next 3 years, and every 6–12 months thereafter.[12] New mass, pain, vascular compromise, and neurologic deficit are indications for immediate clinical examination and imaging.

According to the literature, patients with any advanced-stage tumor and low clinical suspicion for recurrence or with any stage of disease and moderate clinical suspicion of recurrent tumor should undergo PET/CT as an initial investigation, followed by CT, MRI, and US.[2] One could argue which of these modalities, used in clinical practice, is the best to detect occult metastases, not detectable on routine physical examination.

In the current study, we evaluated the diagnostic performance of PET/CT and US in patients with no sign of regional recurrence at the mean follow-up of 10 months. To determine the abnormality on US we relied on lymph node size and shape criteria whereas PET/CT provided additional

information about metabolism and precise localization of the occult recurrence.

Our results show that ultrasound has high diagnostic performance (sensitivity 81%, specificity 87%, accuracy 84%, PPV 83%, NPV 85%) for the detection of cervical lymph node metastases, i.e. regional recurrence. The findings of our study agree with daily practice and literature where US is the most commonly used modality with a high accuracy to detect cervical lymph node metastases.[13] Compared to PET/CT, US has been shown to be as sensitive, specific and accurate, if not superior, in detecting neck node metastases.

The main disadvantages of US compared to PET/CT are the moderate inter-observer variation and imaging limited to soft tissue. On the other hand, US offers numerous advantages over PET/CT. It is less time consuming, inexpensive, repeatable, well tolerated by patients, and does not expose a patient to radiation.

Evaluating the diagnostic performance of PET/CT, this imaging modality was found to be both highly sensitive (86%) for detection of HNSCC recurrences and to have high NPV (89%), but it demonstrated low specificity (82%) and PPV (79%). Our findings support the literature in confirming that PET/CT alone cannot reliably predict the presence of residual cervical metastatic disease, but its negative predictive value (NPV) is high enough to rule recurrence out.[14–18] It indicates that a positive result is not particularly useful to the clinician but a negative one can reliably allow the patient to avoid neck dissection and further imaging.Fused PET/CT offers numerous advantage over other imaging modalities. It is typically applied as a whole-body imaging technique in contrast to regional application of US. It is a relatively standardized technique visualizing both soft and bone structures that can be performed at most referral hospitals. Furthermore, the CT aspects allow for assessment and visualization of PET-negative lesions. General disadvantages of PET/CT include its costs, radiation exposure, use of intravenous contrast, interpretation challenges. The latter include false-positive results that may occur because of infections; a physiologically increased uptake in structures such as palatine tonsils, salivary glands, and masticators, oral cavity, neck, and laryngeal muscles; uptake in reactive nonneoplastic lymph nodes; and, if within 4–6 months after surgery, noninfectious inflammation and granulation at the surgical site (flare phenomenon); false-negative results, on the other hand, can occur if malignancy is present in structures with physiologically elevated metabolism (e.g., tonsillar carcinoma); if tumor size is below the resolution of current PET/CT scanners (typically 8 mm); if the tumor is not FDG-avid; or if a patient is scanned too early after completion of primary treatment.[19–21]

Whether US or PET/CT imaging alone is accurate enough to guide treatment decisions in patients with head and neck malignancies, depends on the ability of these imaging techniques to rule out the presence of occult recurrence. On the basis of this study, we believe that both PET/CT and US with its high NPV are a valuable part of the diagnostic process in patients with no evidence of suspicious lymphadenopathy or mass on the physical examination. However, we can never refrain from biopsy in further treatment planning.

6. Conclusion

This histology-controlled study shows that at present US could be regarded as complementary to PET/CT as a procedure with the highest sensitivity, specificity and NPV for detecting subclinical regional recurrences after HNSCC treatment. These have become routine methods in our institution.

Conflict of interest statement

None declared.

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